ARCHIVES OF PATHOLOGY

VOLUME 45 FEBRUARY 1948 NUMBER 2

A MORPHOLOGIC STUDY OF THE CARDIAC CONDUCTION SYSTEM

V. The Pathogenesis of Heart Block and Bundle Branch Block

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HISTORICAL REVIEW

AT THE end of the first decade of this century the orthodox concepts of the origin of the cardiac impulse and of cardiac conduction were being formed. The formation of the concepts was due to two significant developments in cardiology, viz., the finding of the His [1]-Tawara [2] bundle and the node of Keith and Flack,[3] and Einthoven's [4] invention of the electrocardiograph. The first development led to the theory that the cardiac impulse originates in the muscle fibers of a sinoatrial node and is transmitted to the ventricular myocardium by a special muscular atrioventricular bundle; the second gave investigators a means of depicting accurately the results of experimental attacks on the special conducting tissue.

Experimental Studies.—The effect of ablation of the sinoauricular node was ascertained by several investigators soon after the discovery of the node. But in 1910 the discoverer, Flack,[5] wrote: "With strong clamping sufficient to obliterate the node, little or no effect is produced upon the heart rhythm."

In 1909 Barker and Hirschfelder [6] attempted to determine the function of the His bundle. They made transverse cuts in the left side of

This investigation was aided by grants from the Committee on Scientific Research of the American Medical Association and from the Iowa Methodist Hospital, Des Moines.

1. His, W., Jr.: Arb. a. d. med. Klin. zu Leipzig, 1893, p. 14.
2. Tawara, S.: Das Reitzleitungssystem des Säugetierherzens, Jena, Gustav Fischer, 1906.
3. Keith, A., and Flack, M.: J. Anat. & Physiol. **41**:172, 1907.
4. Einthoven, W.: Arch. internat. de physiol. **4**:132, 1906.
5. Flack, M.: J. Physiol. **41**:64, 1910.
6. Barker, L. F., and Hirschfelder, A. D.: Arch. Int. Med. **4**:193, 1909.

the interventricular septum in 14 animals. In all but 1 atrioventricular dissociation developed. The investigators concluded: "The His bundle plays little if any role in the coordination of the two ventricles."

Two years later Erlanger [7] reported that by applying a fishhook clamp to the base of the aorta and the upper part of the interventricular septum, he had compressed the stem of the His bundle in 17 dogs, in 16 of which complete atrioventricular dissociation had followed. In 1910 Eppinger and Rothberger [8] reported that they had made transverse cuts on both sides of the upper part of the interventricular septum in a number of dogs that were connected to a string galvanometer by an anoesophageal lead. A number of their experiments were unsuccessful, but complete right and left bundle branch block complexes were produced in a few instances. When the cut was made on the left side of the septum, the electrocardiographic complexes became diphasic, having a tall R; when on the right, they became diphasic, showing a deep S. Eppinger and Rothberger stated that they had produced right and left bundle branch block. A little later (1916) Lewis [9] and his associates, employing limb leads, repeated the experiments of Eppinger and Rothberger on dogs and a rhesus monkey. They verified the results of the Viennese investigators and reported that in some dogs and in the monkey the main spike in lead I was upwardly directed when the cut was made on the right side of the septum. In 1921 Wilson and Herrmann,[10] modifying the bundle branch block experiment of Eppinger and Rothberger by compressing the upper part of the septum, produced complete bundle branch block. When compression was released, the electrocardiogram gradually returned to normal. Finally, in 1935, Kountz and associates,[11] employing the technic of Eppinger and Rothberger, were able to produce right and left bundle branch block in perfused human and monkey hearts.

With the exception of Barker and Hirschfelder, the investigators cited had concluded that the conduction disturbances produced were due to injury of the stem or of one of the main branches of the His bundle. It seems to us that the reported facts do not justify this conclusion, because the experimental injury of the His bundle was but a minute fraction of the damage inflicted on the septal myocardium. Our conclusion is: Injury of the upper part of the interventricular septum

7. Erlanger, J.: J. Exper. Med. **8**:8, 1906.

8. Eppinger, H., and Rothberger, C. J.: Ztschr. f. klin. Med. **70**:1, 1910.

9. Lewis, T.: Phil. Tr. Roy. Soc., London, s.B **207**:247, 1916.

10. Wilson, F. N., and Herrmann, G. R.: Heart **8**:229, 1921.

11. Kountz, W. B.; Prinzmetal, M.; Pearson, E. F., and Koenig, K. F.: Am. Heart J. **10**:605, 1935. Kountz, W. B.; Prinzmetal, M., and Smith, J. R.: ibid. **10**:623, 1935.

may bring about the conduction disturbances known as heart block and bundle branch block.

Clinical Studies.—During the second and third decades of the twentieth century, electrocardiography became an integral part of medical practice in clinics where limb leads were used. Since lead III corresponds most nearly to the anoesophageal lead used by Eppinger and Rothberger when they produced bundle branch block, clinical observers interested in disturbances of cardiac conduction assumed that the configuration of the ventricular complexes of lead III determined the location of the revealed bundle branch block; i. e., when a tracing showed the main ventricular spike directed downward in lead III, the block was assumed to be right; conversely, when the spike pointed upward in lead III, the block was assumed to be left. This assumption was strengthened by Eppinger and Stoerck [12] in 1910 when they reported a microscopic study of the right and left bundle branches in 2 cases in which the diphasic ventricular complexes were widened, with a deep S_3. They found that the right branch had been completely interrupted, whereas the left was intact. They concluded that in both cases there was complete right bundle branch block.

A few years later Cohn and Lewis [13] examined 2 cases of heart block. In one they found some increase of fibrous tissue in the region of the stem of the His bundle; in the other, only enlarged veins. Later they [14] examined 4 cases of bundle branch block, concluding: "The conduction problem cannot be solved in the domain of pathologic anatomy."

Meanwhile (1914) Carter [15] had set up criteria for right and left bundle branch block. Three years later Oppenheimer and Rothschild [16] reported that of 62 cases with abnormally prolonged QRS intervals, only 4 fulfilled Carter's criteria of complete right or left bundle branch block. In 11 of their atypical cases of bundle branch block the pertinent tissues were examined grossly and microscopically. All showed increased general myocardial fibrosis, most pronounced subendocardially below the left papillary muscles. They reasoned that the atypical bundle branch complexes depicted arborization block.

In 1920 Fahr [17] reported an analysis of the clinical electrocardiogram; he had decided that the ventricular complexes of right bundle branch block were those of left block, and vice versa. Shortly afterward

12. Eppinger, H., and Stoerck, O.: Ztschr. f. klin. Med. **71**:157, 1910.
13. Cohn, A. E., and Lewis, T.: (*a*) Heart **4**:7 and (*b*) 15, 1912.
14. Cohn, A. E., and Lewis, T.: Proc. New York Path. Soc. **14**:207, 1914.
15. Carter, E. P.: Arch. Int. Med. **13**:803, 1914.
16. Oppenheimer, B. S., and Rothschild, M. A.: J. A. M. A. **69**:429, 1917.
17. Fahr, G.: Arch. Int. Med. **25**:146, 1920.

Oppenheimer and Pardee [18] reported a histologic study of 2 cases of bundle branch block, right in one and left in the other, agreeing with Fahr that in right block the obstructing lesion was found on the right side, the left branch being normal; in left block the obstructing lesion was found on the left side, the right branch being normal. Nevertheless, other students of the morbid anatomy of bundle branch block (Taussig [19] and Hill [20]) continued to find the causal lesion of the common type of bundle branch block on the right side of the septum. However, at the end of the third decade investigators in Michigan—Barker, Macleod and Alexander [21]—reported a reevaluation of bundle branch complexes based on electrocardiographic curves obtained by direct leads from the exposed human heart. They found that the complexes of the common type of bundle branch block represent interruption of the wave of excitation in the left ventricle, and those of the less common type, interruption in the right.

Two years later (1931) Mahaim's [22] monograph appeared. Mahaim found that heart block was due to interruption of both branches of the His bundle and that bundle branch block was associated with lesions of both branches. However, the interrupting lesions in the common type occurred on the right side, whereas in the less common type they occurred on the left.

Finally, in 1938, Yater's [23] study of the genesis of bundle branch block was published. Yater, like Mahaim, found bilateral lesions in both types of bundle branch block, but he found the completely interrupting lesions located in the left branch in the common type and in the right branch in the rare type. Mahaim and Yater rejected many conclusions concerning the morbid anatomy of conduction disturbances which did not agree with their own because they considered that the abnormalities had been incompletely studied.

Our Investigations.—In 1939, one of us (D. J. G.) became interested in locating and studying the lesions in a case of the common and a case of the less common type of bundle branch block. To his surprise and dismay he could not even find the His bundle. The failure led to the present series of studies of cardiac conduction. One of us (D. J. G.)

18. Oppenheimer, B. S., and Pardee, H. E. B.: Proc. Soc. Exper. Biol. & Med. **17**:177, 1919-1920.

19. Taussig, H. B.: Bull. Johns Hopkins Hosp. **45**:40, 1929.

20. Hill, I. G. W.: Quart. J. Med. **24**:15, 1930.

21. Barker, P. S.; MacLeod, A. G., and Alexander, J.: Am. Heart J. **5**:720, 1930.

22. Mahaim, I.: Les maladies organiques du faisceau de His-Tawara, Paris, Masson & Cie, 1931.

23. Yater, W. M.: Arch. Int. Med. **62**:1, 1938.

and A. T. A. Glomset [24] undertook to look for and to describe the sinoatrial node in man, dog, monkey, horse, sheep, cattle and swine but failed to find a sinoatrial node. The histologic composition of the walls and the floor of the sulcus is identical with that of the other grooves which are formed by the entering veins and the atrial wall.

Subsequently the Glomsets searched for an atrioventricular conducting bundle in the same species. Again they [25] failed. Such a bundle was not found in any of the hearts examined. In the hearts of the cloven-hoofed animals and the horse there exists a distinct bundle. It is entirely ventricular. It is vestigial in the horse, consisting mostly of fibrous tissue. The Purkinje bundle is separated from the rest of the myocardium by a distinct connective tissue sheath. Its parenchyma is composed about half and half of modified muscle cells (Purkinje's fibers) and nerve tissue. The muscular part of the bundle has its origin in the atrioventricular fibrous ring just behind the central fibrous body. In sheep and cattle the fibers interlace to form a lump (the node of Tawara). As the muscle strands of this node approach the canal in the central fibrous body, they join the nerve trunks to form the Purkinje bundle. At this junction the muscle cells abruptly change into the large binucleated Purkinje fibers. The nerve trunks are composed of the axis-cylinders of numerous nerve cells lying in the atrioventricular groove on top of the ventricular septum. The composite bundle runs forward on the top of the septum, dividing into a right and a left branch at the lowest point of the septum membranaceum. Each branch subdivides at the level of the papillary muscles to form subendocardial and intramyocardial networks. No structure analogous to the Purkinje bundle and networks exists in man, dog or monkey.

The bundle which has been extensively studied as the His bundle in man and dog is an insignificant muscle fasciculus (the ridge fasciculus [26]) having its origin in the atrioventricular fibrous ring just behind the canal of the central fibrous body. It, like the Purkinje bundle, runs through this canal and continues forward on top of the septum; it then passes downward without branching to form an insignificant part of the musculature of the right side of the septum. The fasciculus runs superficially for a short distance below the base of the tricuspid valve, where it becomes overlaid by other muscle fibers. It continues to the base of the papillary muscle and takes a small part in the formation of the latter. Structurally and tinctorially the ridge fasciculus is identical with the neighboring muscle bundles.

24. Glomset, D. J., and Glomset, A. T. A.: Am. Heart J. **20**:389, 1940.
25. Glomset, D. J., and Glomset, A. T. A.: Am. Heart J. **20**:677, 1940.
26. Glomset, D. J., and Birge, R. F.: Am. Heart J. **29**:526, 1945.

We also noted, as have others (Woollard,[27] Perman [28] and Fakutake [29]), that all the hearts examined contain a rich, well developed nervous system, the cells of which are found underneath the pericardium of the atrium and in the atrioventricular groove. The nerve processes of the cells form numerous nerve trunks that follow the coronary arteries in the ventricles and eventually break up into an endocardial and a pericardial network of nerve fibrils.

PRESENT STUDY

From the aforementioned observations it seems obvious that the conduction abnormalities called heart block and bundle branch block cannot be due to lesions blocking the wave of excitation in a special conducting bundle. However, experimental injury of the upper part of the septum does produce heart block and bundle branch block. Is there any causal relation between abnormalities of conduction and the lesions involving the myocardium of the upper part of the septum in man, and what relation do lesions found elsewhere in the ventricles bear to atrioventricular dissociation and delay of intraventricular conduction? In the present communication we record the results of our endeavor to find answers to these questions by an analysis of the lesions reported by 57 observers and our own findings in 28 human hearts.

Our material consists of hearts obtained in 28 clinical cases in which the principal cause of death was heart failure. Seven of the cases, in which the P-R and QRS intervals were normal were studied as controls. Seven cases were instances of left and 5 of right bundle branch block; in 8 cases the block was indeterminate; the remaining case, an instance of heart block, is not tabulated. All hearts were studied according to the following plan.

TECHNIC

Each heart was obtained as soon as possible after death, washed, and submerged in 4 per cent formaldehyde solution, in which it remained until properly fixed (five to fourteen days); it was then grossly examined according to the outline given in figure 1.

Blocks were removed from the localities of the heart shown in figure 2. In order to facilitate orientation, the lower end of the block was cut shorter and thinner than the upper, and the posterior edge was notched. The blocks were lettered, and the letter and the number of sections to be cut and stained were recorded on a work sheet similar to figure 2. Most of the sections were stained by the iron-hematoxylin procedure. Only in rare instances were a fat stain and a trichrome stain employed. The observations made on each microscopic section

27. Woollard, H. H.: J. Anat. **60**:345, 1925.

28. Perman, E.: Ztschr. f. d. ges. Anat. (Abt. 1) **71**:382, 1924.

29. Fakutake, K.: Ztschr. f. d. ges. Anat. (Abt. 1) **76**:592, 1925.

were noted, and when the examination of a heart was completed, the gross findings and the microscopic observations were recorded on a work sheet similar to figure 2.

HEART NO. 144X

Name *McC*..... Sex *♂*

Autopsy No. *159-46* Hospital No. *39143* Age *54*

Date *7-21-45*

Weight *860 Gm.* Fat *Normal*

Transverse diameter *16.5* Left midline *11.0* Right midline *5.5*

Left ventricle *3.0* Right vent. *10.0* Right atrium *3.5*

Dilatation: Right aur. *2* Right vent. *2* Left aur. *2* Left vent. *3*

Hypertrophy: Right aur. *3* Right vent. *3* Left aur. *2* Left vent. *3*

Right ventricle: Depth *9.5* Thickness *0.9* Circum. *17* Right branch *4*

Left ventricle: Depth *10* Thickness *2.2* Circum. *13* Left branch *6*

Septum: Thickness *2.1* Deviation *R*

Valves: Tricuspid *n* Pulmonary *n* Aortic *n* Mitral *n*

Coronary arteries:	Anterior descending	Left circumflex	Right
	Size *n* Distribution *Apex*	Size *2* Distribution *Large branches to ant. and to post. wall Posterior interventricular sulcus*	Size *n* Distribution *Posterior interventricular sulcus*
	Lesions *2*	Lesions *4*	Lesions *4*

Artery of node	Accessory branches	Septal branches
Origin *Right coronary*	*0*	Normal
Distribution *2 branches to septum*		
Lesions *0*		

Myocardium: *Small area of fibrosis, L. V. near septum. Small infarct post. base*

Node, bundle and branches: *n*

Remarks: *Mural thrombus, base L. V.*

(Use reverse for description of blocks)

Fig. 1.—Work sheet of case 144X (typical bundle branch block), on which measurements and gross lesions are recorded.

THE GROSS FINDINGS

The weight of the heart, the thickness of the walls and the depth and the circumference of the chambers were included in the study in order to determine the degree of hypertrophy and dilatation present.

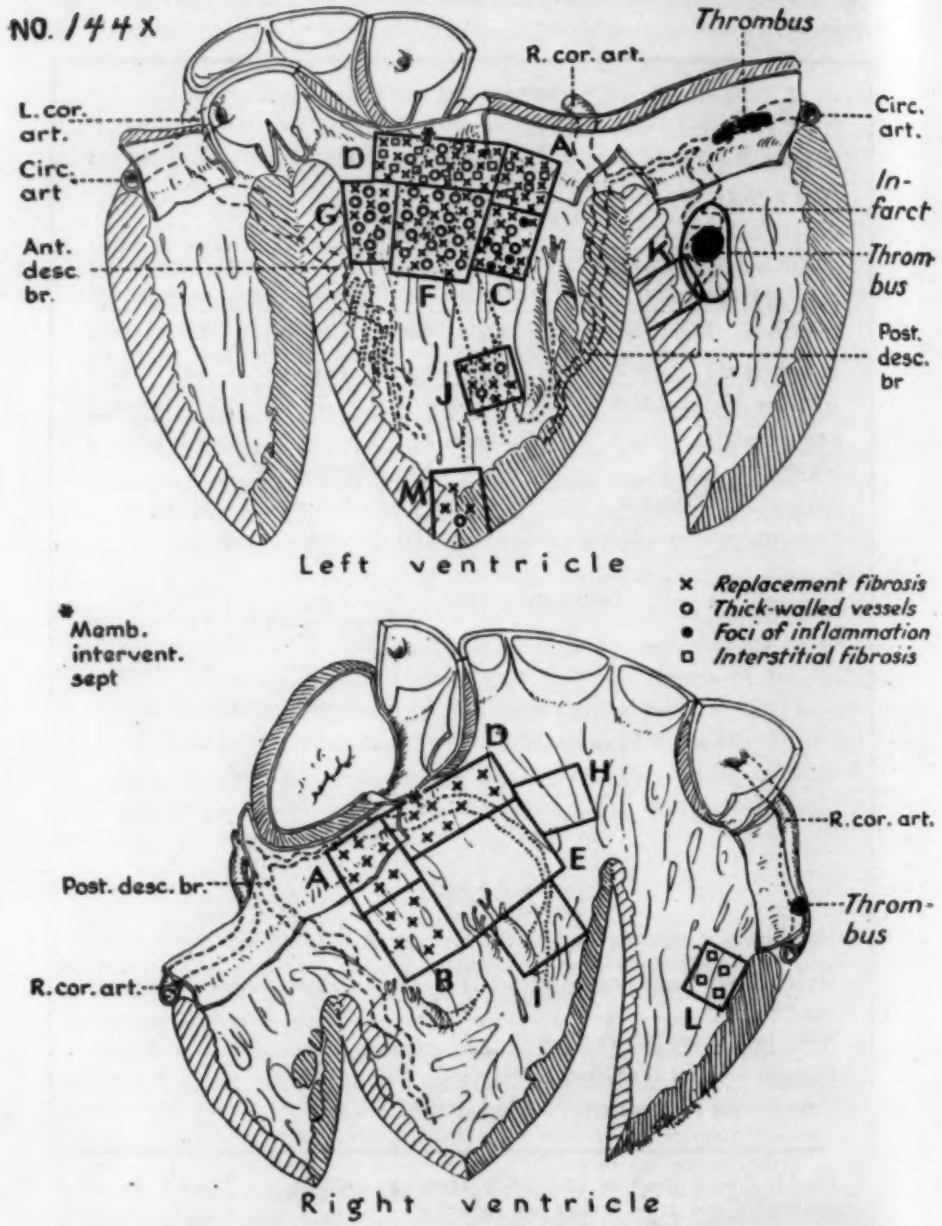

Fig. 2.—Work sheet of case 144X showing locations and types of microscopic lesions.

Einthoven [30] found that preponderance electrocardiograms reflected hypertrophy of one or the other of the ventricles; Lewis [31] determined that hypertrophy increased the length of the QRS interval; Wilson and Herrmann [32] corroborated Lewis' findings, but found that hypertrophy alone could not account for either right or left bundle branch block. Glomset, Glomset and Birge [33] postulated that hypertrophy with unilateral dilatation might account for right or left bundle branch block.

The distances from the lowest point of the septum membranaceum to the base of the posterior left papillary muscle and the base of the right papillary muscle were measured, because Fahr [17] had used these measurements as a part of the basis of his theoretic analysis of the electrocardiogram. We found that on the left side the distance from the lowest point of the septum membranaceum to the base of the posterior papillary muscle varied from 1.9 to 7.5 cm. in controls, from 4.8 to 7 cm. in left bundle branch block, from 3 to 6 cm. in right bundle branch block and from 4 to 5.5 cm. in indeterminate block. On the right side similar measurements varied from 2.2 to 4.5 cm. in left bundle branch block, from 1.5 to 4.5 cm. in right bundle branch block and from 2.2 to 4 cm. in indeterminate block. The thickness of the septum was measured in each heart because Willius [34] postulated that the thickness of the septum plays a role in determining the intervals in bundle branch block. In our cases the thickness of the septum varied from 1 to 2.4 cm. in the controls, from 1.8 to 2.8 cm. in left bundle branch block, from 1.2 to 2 cm. in right bundle branch block and from 1 to 2 cm. in indeterminate block. It therefore appears that neither the distances from the septum membranaceum to the bases of the papillary muscles nor the thickness of the septum has any influence on the electrocardiographic patterns of the various types of blocks. The pattern of the coronary arteries was noted in order to determine the relationship of disease of these arteries to the myocardial lesions.

THE MICROSCOPIC OBSERVATIONS

Before we proceed to a general description of the microscopic lesions of the hearts studied, it may be well to describe the human "Purkinje tissue."

Human "Purkinje Tissue."—In his original communication Purkinje [35] stated that the large binucleated cells lying in rows under-

30. Einthoven, W.: Arch. f. d. ges. Physiol. **122**:517, 1908.

31. Lewis, T.: Heart **5**:367, 1913-1914.

32. Wilson, F. N., and Herrmann, G. R.: Heart **15**:135, 1930.

33. Glomset, D. J.; Glomset, A. T. A., and Birge, R. F.: Am. Heart J. **28**: 348, 1944.

34. Willius, F. A.: Am. Heart J. **1**:576, 1926.

35. Purkinje, J. E.: Arch. f. Anat., Physiol. u. wissensch. Med. **12**:281, 1845.

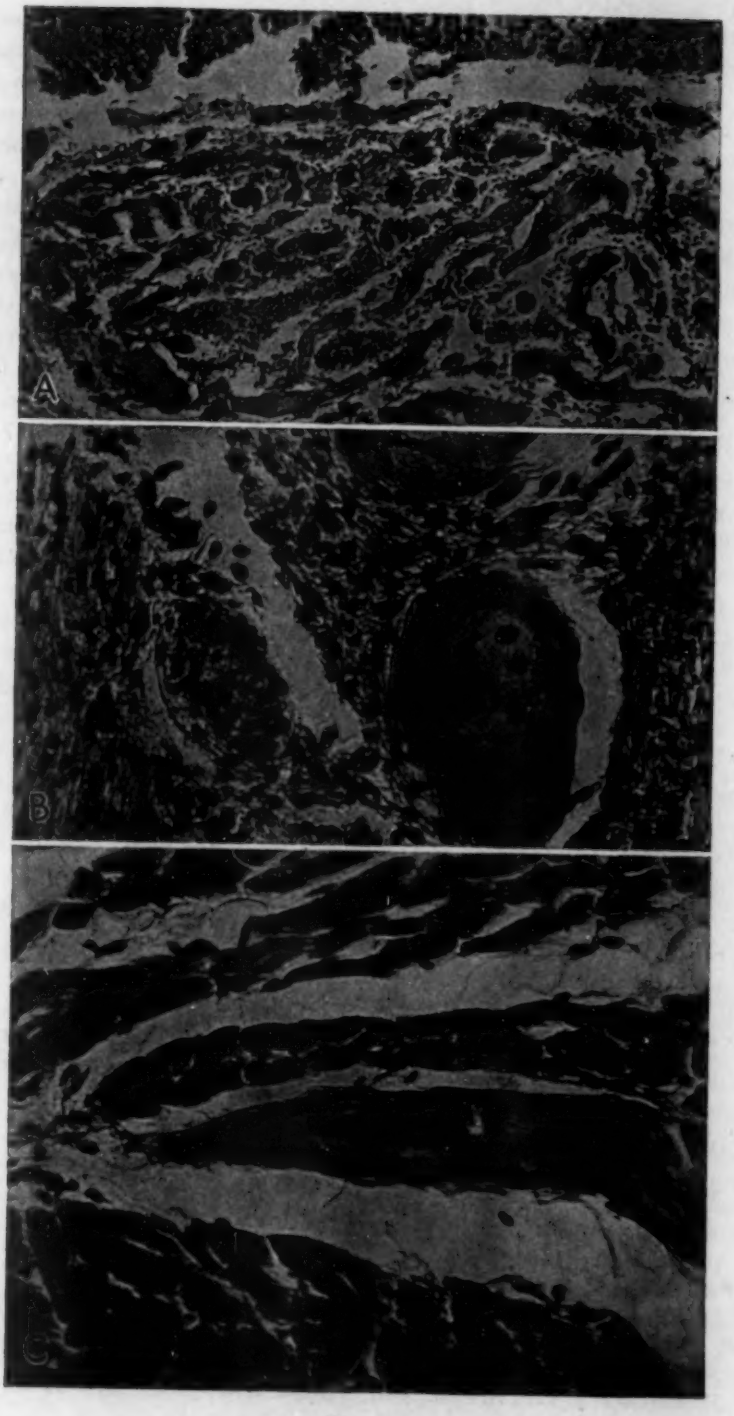

Figure 3

(See legend on opposite page)

neath the ventricular endocardium in the ungulates do not exist in man or dog. Nevertheless, Tawara [2] described not only Purkinje cells but a bundle (the His bundle) and a network of such cells for both human and canine hearts. According to Tawara, the bundle and the network are structurally similar to the bundle and the network of the ungulate heart. Since 1907 a number of investigators have described human Purkinje tissue. The most accurate description, in our opinion, is that of Todd,[36] whose article also contains a number of photomicrographs showing clearly the structure of the human Purkinje cells. Todd found such cells in the myocardium of all the chambers of the heart. He also found, as had Tawara, that the human Purkinje cells change imperceptibly into ordinary muscle fibers and, therefore, concluded that all cardiac muscle fibers originate from Purkinje fibers. It seems to us that this is but another way of saying that human Purkinje cells are ordinary muscle fibers, since a true ungulate Purkinje cell does not "change back" into a myocardial fiber. In man and dog the muscle fibers called "Purkinje cells" do occur in all the cardiac chambers. They are most abundant and therefore best studied underneath the endocardium of the left side of the interventricular septum (fig. 4). These cells are slightly swollen ordinary cardiac fibers which in longitudinal section look beaded. Their diameters are but a few microns greater than those of ordinary muscle cells of the same heart. In blocks obtained from hearts shortly after death and properly fixed, the fibers are morphologically and tinctorially identical with the other myocardial elements. However, when fixation is delayed, the swollen cells have a central clear zone, which in cross section gives them the appearance of hollow cylinders, a fact first noted by Moenckeberg,[37] who considered the clear zone to be glycogen or fat. But the clear zone takes neither fat nor glycogen stains, and its diameter, as well as the number of cells showing the zone, increases with the hours between death and fixation of the tissue; hence, we believe the clearness to be due to postmortem degeneration. When a fasciculus containing the swollen muscle cells enters the deeper portions of the myocardium

36. Todd, T. W.: Specialized Systems of the Heart, in Cowdry, E. V.: Special Cytology, ed. 2, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 1175.

37. Moenckeberg, J. G.: Untersuchungen über das Atrioventrikulärbündel im menschlichen Herzen, Jena, Gustav Fischer, 1908.

EXPLANATION OF FIGURE 3

Purkinje tissue in ungulates: *A*, right branch near the moderator band, ovine (× 90). Note nerve tissue and binucleated Purkinje cells.

B, Purkinje strand, left branch, swine (× 350). Note adjacent nerve trunks.

C, terminal Purkinje strand, deep in myocardium, bovine (× 350). Note connective tissue separating the strand from the rest of the myocardium.

and becomes compressed by neighboring muscle bundles, the swollen appearance disappears; i. e., "they are changed into ordinary muscle fibers"!

Replacement Fibrosis.—The most commonly encountered and perhaps the most significant lesion observed in heart block and bundle branch block appears to be a patchy necrobiosis of the myocardial elements. This lesion has been found by many investigators in cases in which conduction disturbances were present during life. Various descriptive names have been given to this morbid process, viz., "patchy sclerosis," "fibrosis," "replacement fibrosis" and "ischemic fibrosis." We prefer the term "replacement fibrosis." The lesions seem to evolve in this manner: At first the affected muscle cells undergo atrophy; subsequently striations and nuclei are lost; then the sarcoplasm disappears, leaving only the shadows of the destroyed muscle fibers; finally the shadows disappear, leaving the fibrous tissue which once supported the now destroyed myocardium. This fibrous tissue is poor in cells (fig. 5).

The extent of myocardial involvement varies from partial destruction of a few muscle strands within a few widely scattered muscle bundles to involvement of two or more of the cardiac muscle bands. For the purpose of evaluation we have graded the involvement as (1) minimal, in which only two or three strands are affected, (2) moderate, in which several muscle fasciculi have been partially destroyed in many parts of the septum as well as in other parts of the myocardium, (3) marked, in which many groups of muscle fasciculi are involved throughout the ventricles, (4) maximal, in which two or more muscle bands, such as the superficial and deep bulbospiral muscles (Robb[38]), are extensively destroyed, and the process extends through the entire septum.

Vascular Changes.—Within the replacement fibrosis or in its environment there invariably occur small arteries having thickened walls. The thickening, which involves the intima and the media, is sometimes concentric but may be eccentric, giving the appearance of being pushed into the lumen of the vessel (fig. 6). The involvement is segmental and may be found in large and small arteries of the septum. In some arteries the proliferative changes are cellular (fig. 6); in others, fibrous. The changes invariably encroach on the lumens of the affected vessels. The encroachment varies from minimal to complete. The degree of arterial involvement is in direct ratio to the extent of the replacement fibrosis. When a large septal artery is affected, the fibrotic changes are more scattered than when only the smaller vessels show obliterative changes. Since the changes are rarely found where replacement fibrosis is absent, and the numbers of the affected vessels and the degree of

38. Robb, J. S.: M. & S. Year-Book, Physicians Hosp. **1**:210, 1929.

involvement run pari passu with the extent of the replacement fibrosis, it appears that these arterial lesions are responsible for the necrobiosis and the fibrosis.

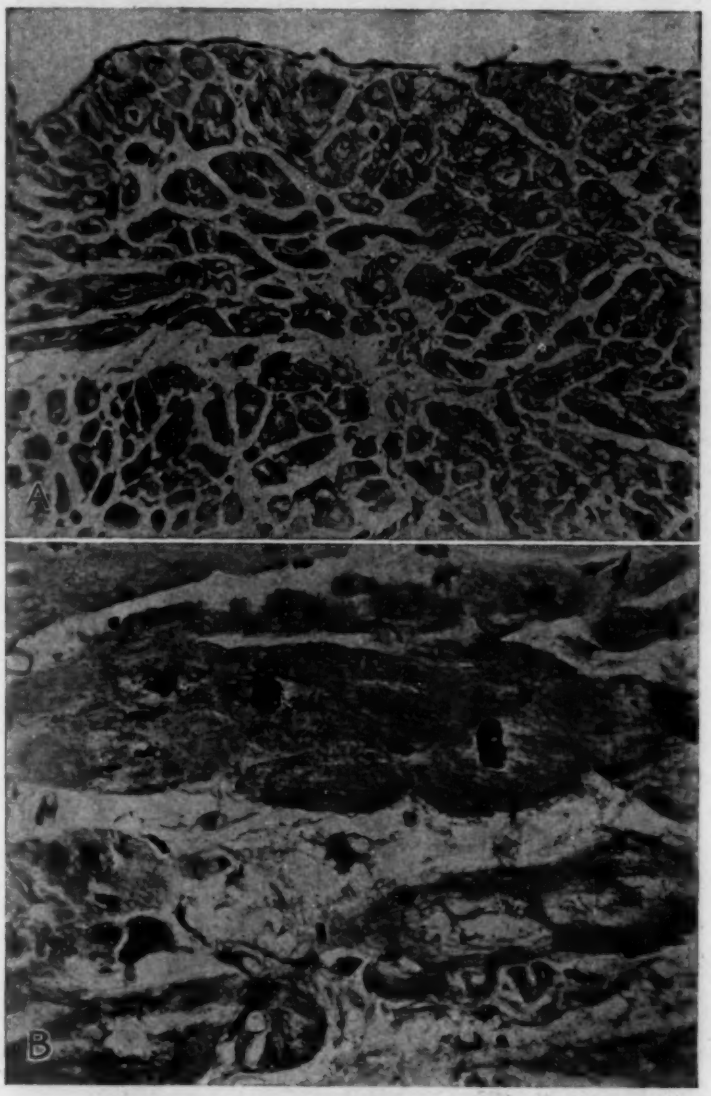

Fig. 4.—Human "Purkinje tissue": *A*, subendocardial, in left ventricle (× 350). Note that it changes "imperceptibly" into ordinary muscle fibers. *B*, muscle fiber from the same locality as *A* (× 700). Note the swollen appearance.

Other Microscopic Lesions Encountered Within the Myocardium.—In addition to replacement fibrosis, a variety of other microscopic morbid changes occur within the myocardium of the examined hearts.

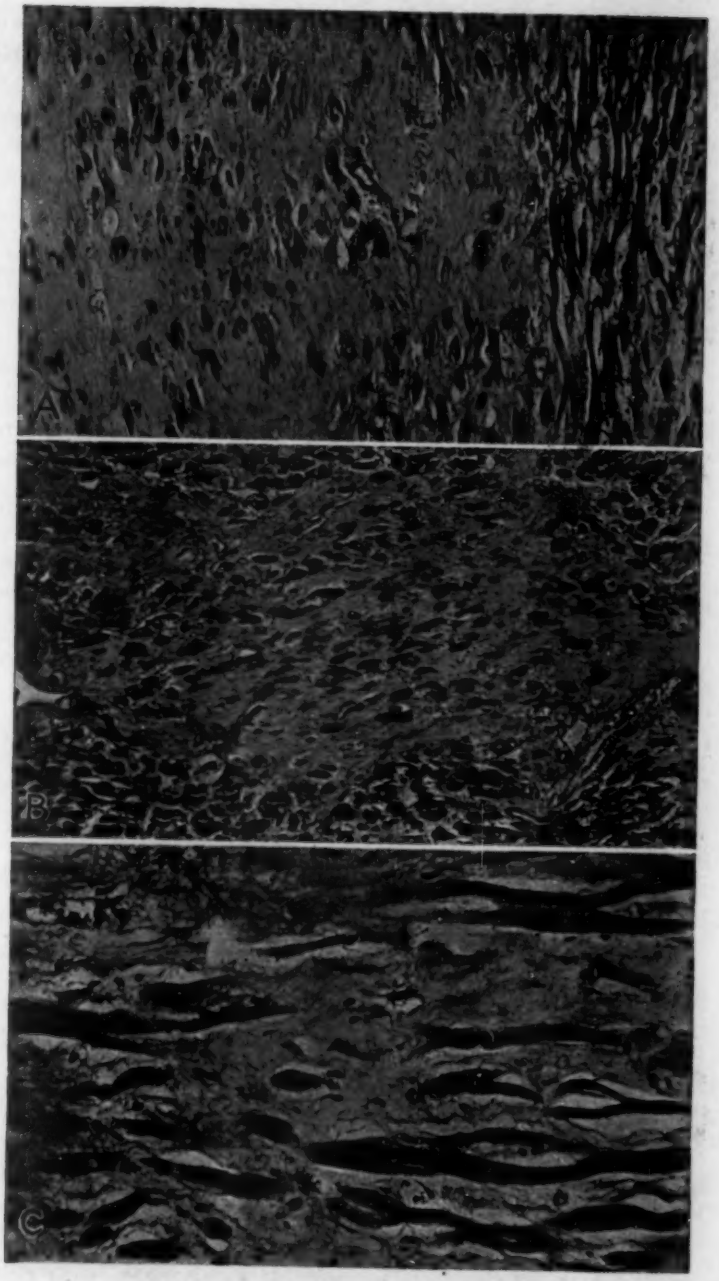

Fig. 5.—Marked replacement fibrosis (*A* and *B*, × 150; *C*, × 350).

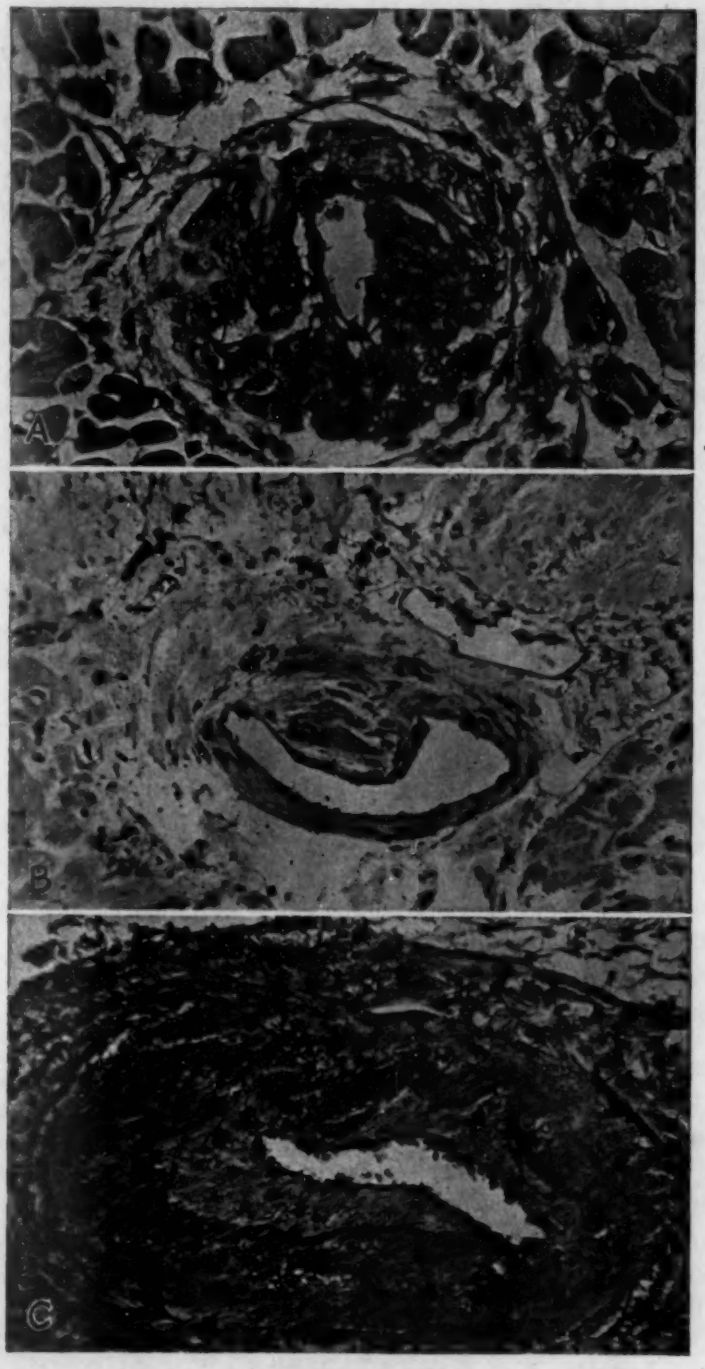

Fig. 6.—Various types of arterial changes occurring in and about replacement fibrosis.

These lesions may or may not be a factor in the genesis of heart block or of bundle branch block. No special attention was given to the minute structure of the atheromatous lesions of the coronary arteries because the microscopic features of atheromas have been described repeatedly by able observers. Nor did we concern ourselves with a description of the microscopic changes occurring in the infarcted myocardium. However, it was surprising to note the width of the zone of the injured myocardium surrounding the visible infarct.

Hearts from persons having a definite history of attacks of rheumatic fever many years prior to death with a subsequent long period of freedom from signs and symptoms of infection contained not only acellular patches of perivascular fibrosis but also, here and there, typical Aschoff bodies and areas of round cell infiltration. In the hypertensive hearts, definite arteriolar sclerosis, so conspicuous in the arterioles of the hypertensive kidney, occurred.

ANALYSIS OF THE LESIONS FOUND IN HEART BLOCK AND BUNDLE BRANCH BLOCK

Investigators who believe that a special atrioventricular conduction bundle exists in man have searched in the upper part of the interventricular septum for the causal lesions of atrioventricular dissociation and of intraventricular conduction delay. Most of them have made a meticulous study of hundreds and even thousands of serial sections cut from the strips of septal myocardium where in the ungulates the Purkinje bundle is located. The majority of investigators have found the causal lesions of heart block either in the stem or in both branches of the His bundle, and the blocking lesions of bundle branch block in the right or the left branch of this bundle. Two (Oppenheimer and Rothschild [16]) found the causal lesions of arborization block in the left subendocardial myocardium below the papillary muscles.

To us it is inconceivable that even complete destruction of the tiny "ridge fasciculus" or of one or more tiny muscle strands of the left side of the septum could produce demonstrable disturbances of conduction. Nevertheless, the permanent forms of both heart block and bundle branch block nearly always occur in sick hearts, which contain a variety of demonstrable morbid changes. These have been encountered and described by other seekers. We, too, have observed various types of lesions in the 28 hearts which form the basis of this study.

An analysis of the information obtained from 76 cases already recorded in medical literature and our own findings and observations will now be attempted.

The Tables.—Tables 1 and 2 contain data concerning 7 control hearts. In tables 3 to 6 the A and B sections contain information

obtained from medical literature; the C and D sections, comparable data recorded in our own cases. The extent of abnormality recorded has been graded 1 to 4. The descriptive grading employed for replacement fibrosis has already been explained. Hypertrophy, dilatation and atherosclerosis have been graded similarly:

Hypertrophy: grade 1, minimal (hearts weighing between 350 and 450 Gm.); grade 2, moderate (between 450 and 550 Gm.); grade 3, marked (between 550 and 700 Gm.); grade 4, maximal (more than 700 Gm.).

Dilatation: grade 1, minimal, scarcely perceptible dilatation of a ventricle; grade 2, moderate; grade 3, marked; grade 4, maximal dilatation.

TABLE 1.—*Seven Control Cases: Lesions Occurring in the Upper Part of the Ventricular Septum*

Case	Clinical Diagnosis	Gross Lesions	Replacement Fibrosis	Perivascular Connective Tissue	Other Lesions
107 x	Hypertensive cardiovascular disease; left ventricular strain	0	0	2	0
110 x	Hypertensive cardiovascular disease	0	1	0	Chronic endocarditis
3 x	Coronary heart disease.....	0	1-2	0	0
101 x	Coronary heart disease.....	0	1	0	Endocarditis
108 x	Rheumatic heart disease.....	0	0	2 rheumatic Aschoff bodies	0
113 x	Hypertensive cardiovascular disease	0	1	1	Thickening of walls of blood vessels
120 x	Cardiac hypertrophy (?).....	0	1	0	0

Atherosclerosis: grade 1, minimal, with only a few atheromas, not encroaching on an arterial lumen; grade 2, moderate, with a number of atheromas encroaching to some extent on arterial lumens; grade 3, marked, in which lumens are much narrowed in segments of an artery; grade 4, with occlusion present.

In order to facilitate analysis of the data gleaned from the literature for a comparison with our own observations, the tables have been arranged according to one pattern. In the A and C sections of tables 3 to 6 are cataloged the lesions observed above the bases of the papillary muscles in the interventricular septum. In the B and D sections of these tables the essential morbid changes observed in the rest of the ventricles are listed.

Controls.—In tables 1 and 2 are arranged the lesions found in 7 hearts whose P-R and QRS intervals were normal. The lesions

were studied in the same manner as those of the other hearts in our series. A glance at table 1 reveals that in no instance were there significant gross or microscopic lesions in the upper part of the septum; furthermore, table 2 shows that all of the hearts were hypertrophied, 5 markedly so. In case 113x hypertrophy of the left ventricle was maximal and dilatation moderate, whereas both hypertrophy and dilatation of the right ventricle were only moderate; yet the QRS interval was only 0.08 second. Five hearts had no significant changes in the coronary arteries. In 2 there was grade 4 atherosclerosis with infarcts in the lower part of the intraventricular septum.

Heart Block.—The lesions observed in 29 cases of heart block are listed in tables 3 A and 3 B. It is significant that in 10 cases there was associated bundle branch block. Table 3 A shows that in 19 of the 29 instances there were extensive gross lesions in the upper part

TABLE 2.—*Seven Control Cases: Lesions Occurring Elsewhere in the Ventricles*

Case	Hypertrophy	Dilatation	Coronary Athero-sclerosis	Infarcts	Other Lesions
107 x	L.V. 3, R.V. 1	L.V. 0, R.V. 0	2	0	0
110 x	L.V. 3, R.V. 2	L.V. 3, R.V. 3	1	0	0
6 x	L.V. 3, R.V. 1	L.V. 2, R.V. 0	4	Lateral and posterior walls, involving lower part of septum	Mural thrombosis
101 x	L.V. 3, R.V. 2	L.V. 4, R.V. 3	4	Anterior and lateral walls, involving septum	Thickening of endocardium
108 x	L.V. 2, R.V. 2	L.V. 1, R.V. 2	1	0	Adventitial thickening of blood vessels
113 x	L.V. 4, R.V. 2	L.V. 1, R.V. 2	1-2	0	Arteriolar sclerosis
120 x	L.V. 2, R.V. 1	L.V. 4, R.V. 4	0-1	0	Mural thrombus

of the septum—in 6, infarcts; in 4, calcification; in 3, granulomatous lesions; in 5, patchy fibrosis; in 1, scarring. In 21 of the 29 cases the lesions involved the branch strips. In 9 the morbid changes in the branch strips were the only ones recorded; in the remaining 12 the morbid changes in the branch strips occurred in conjunction with lesions observed elsewhere in the septum. In 4 of these 12 cases bundle branch block was present. It may be significant that in 2 of the cases of heart block no gross or microscopic lesions were observed in the upper part of the septum. If we add to the findings reported in the literature our single case of heart block, in which a large infarct involved the upper part of the septum, it may be concluded that in 10 per cent of the cases of heart block the causal lesion was not found in the upper part of the interventricular septum.

The heart size is recorded for 21 of the listed cases. In 8 hypertrophy was either minimal or absent; in 13, moderate or maximal. The condition of the coronary arteries is recorded for 22 hearts: normal

in 2, minimal to moderate in 9, markedly narrowed or occluded in 11. Three infarcts are recorded: one in the midpart and two in the lower part of the septum.

Left Bundle Branch Block.—We have reviewed the morphologic observations made in 24 cases of the more common type of bundle branch block which, according to the American consensus, is left bundle branch block. Eleven instances in which there were gross lesions are recorded in tables 4 A and 4 B. In 3 cases these were infarcts; in the others, scars, patches of fibrosis or necrosis. It is in cases of this form of block that the most strenuous effort has been made to find the causal lesions by studying serial sections. In general, the observer seems to have found the blocking lesion on the side where he expected it to be from the electrocardiographic pattern. One case was reported in which both branches were destroyed; in 8 cases the right branch was interrupted; in 6 the left branch was blocked; in 4 both branches were practically normal; in 7 the right branch was normal; in 6 the left was normal; in 11 the lesions were bilateral.

In tables 4 C and 4 D we have listed observations made by us in 5 cases of typical and 2 cases of early left bundle branch block. In the 5 typical cases there were no gross lesions. In one of the early cases (QRS, 0.11 second) an infarct was present; in the other (QRS, 0.10 second), a case in which rheumatic heart disease was also present, with aortic stenosis, there were no gross lesions, but the replacement fibrosis and perivascular connective tissue were moderate to marked. In all the 5 typical cases the replacement fibrosis was maximal in the left ventricle; it was moderate in 1, marked in 1 and maximal in 3, in the right ventricle.

It is difficult to evaluate the 18 cases in table 4 A in which the examination seems to have been practically limited to the branch strips. Of course, we, too, have followed the custom originated by His of making serial sections of the bundle strip regions but have found it a physical impossibility to examine every section; at most, only 1 in 10 was studied. From the examination of our serial sections it may be concluded: 1. It is impossible to describe a left branch in man, because it does not exist. When attempts are made to follow the fasciculi which originate in the fibrous ring from which the left branch should spring, it is found that the fasciculi are identical with their fellows in every respect, take various directions in individual hearts and soon become overlaid by other muscle fibers which have their attachments in the endocardium. The result is that the traced bundles either run out of the block or become irrecoverably mixed with strands from other fasciculi. This structural peculiarity accounts for the comparatively monstrous appearance of the left branch as sketched by Mahaim. 2. On the right side one finds it easier to make observations of the ridge fasciculus by

TABLE 3A.—*Heart Block: Lesions Occurring in the Upper Part of the Ventricular Septum (Data Obtained from Medical Literature)*

Author	Case	Gross Lesions	Microscopic Lesions			Associated Abnormalities
			Stem	Right Branch	Left Branch	
Cohn and Lewis[12b]	..	Syphilitic aneurysm involving upper part of septum	Dense fibrosis at termination	Connective tissue replacement of upper part	Connective tissue replacement of upper part	Bundle branch block, right
Davis, A. C., and Smith, H. L.: Am. Heart J. 9 : 81, 1933	..	.....	Cellular infiltration			Bundle branch block, right
Schwartz, S. P.: Am. Heart J. 11 : 554, 1936	5	Infarct involving left ventricle and upper septum	Numerous fibrous areas			
	6	Recent infarct of left ventricle	Marked subendocardial scars in right and left ventricles			
Strauss, S. P., and Langendorf, R.: Am. J. M. Sc. 205 : 233, 1943	..	.....	.....	Fibrosis	.....	Bundle branch block, right and left
Yater, W. M.; Cornell, V. H., and Claytor, T.: Arch. Int. Med. 57 : 132, 1936	1	.....	Normal	Destruction of upper third	Fibrotic destruction of upper half	
	2	.....	Slight fibrosis	Fibrosis of upper third	Dense fibrosis of upper half	Bundle branch block, left
	3	Scars in base of septum	Normal	Fibrosis of upper part	Upper part extremely fibrotic	Indeterminate block
Deneke, T.: Arch. f. klin. Med. 89 : 39, 1906	..	Diffuse fibrosis	.....	Destroyed by fibrosis	Destroyed by fibrosis	
Gaisboeck, F., and Jurak, L.: Zentralbl. f. Herzkr. 7 : 37 and 49, 1915	..	Fibrocalcification	Fibrocalcification			
Biedl, A., and Rihl, J.: Zentralbl. f. Herzkr. 8 : 71, 1916	..	.....	.....	Damaged; fibrosis	Destroyed by fibrosis	Bundle branch block, right and left
Moenckeberg, J. G.: Beitr. z. path. Anat. u. z. allg. Path. 63 : 77, 1916	..	Septal fibrosis	.....	Destroyed by fibrosis	Involved by fibrosis	Bundle branch block, right

Sisto, P.: Mal. d. cuore **6**: 6, 1922.....	..	Fibrosis	.....	Fibrosis	Fibrosis	
Mahaim [22]	..	Fibrosis of myocardium	.....	Fibrosis	Fibrosis	Bundle branch block, left
	2	.....	.....	Fibrosis	Fibrosis	Bundle branch block, indeterminate
Gerhardt, D.: Deutsches Arch. f. klin. Med. **106**: 462, 1912	1	Infarct of upper part of septum	.....	.....	Interrupted by fibrosis and necrosis	
	2	Calcification	.....	—Partially destroyed by calcification—		
Appelbaum, E., and Nicolson, G. H. B.: Am. Heart J. **10**: 602, 1935	1	Calcification of upper part of septum				
	2	Infarct				
Digregorio, N. J., and Crawford, J. H.: Am. Heart J. **17**: 114, 1939	..	Infarct of upper part of septum	—————————Infarct—————————			
Hume, W. E.: Heart **5**: 149, 1913.....	..	.....	————————————Normal————————————			
Stengel, A.: Am. J. M. Sc. **130**: 1083, 1905	..	Atheromatous patch over His bundle				
Jervell, A.: Acta med. Scandinav., 1935, supp. 68, p. 1	..	Infarct				
Cohn and Lewis [13a].....	..	.....	——Fibrous tissue; blood sinuses——		.....	
Gertz, G.; Kaplan, H. A.; Kaplan, L., and Weinstein, W.: Am. Heart J. **16**: 225, 1938	..	.....	.....	Fibrous tissue interrupting conducting fibers		Bundle branch block, left
Heninger, B. R., and Dickens, K. L.: Ann. Int. Med. **10**: 696, 1936	..	Calcification	————————————Normal————————————			
Menon, T. B., and Rao, C. K. P.: Am. J. Path. **21**: 1193, 1945	..	Two whitish nodules in septum membranaceum and below	——————Nodes—typical tuberculosis.——————			
Dreyfuss, F.: Brit. Heart J. **7**: 128, 1945	..	.....	——————Normal stem and branches——————			
Major, R. H.: Arch. Int. Med **31**: 837, 1923	..	Gumma	————————————Gumma..————————————			Diabetes

TABLE 3B.—*Heart Block: Lesions Occurring Elsewhere in the Ventricles (Data Obtained from Medical Literature)*

Author *	Case	Gross Lesions: Hypertrophy	Dilatation	Coronary Athero-sclerosis	Infarcts	Other Lesions	Microscopic Lesions
Cohn and Lewis [12b]	..	L.V. 4, R.V. 4	L.V. 2, R.V. 1	2			
Davis and Smith *	..	0 0	L.V. 1, R.V. 0	0			Leukocytic infiltration of septum and right ventricle
Schwartz *	5	L.V. 3, R.V. 3	....	3			Fibrous areas
		3	1	4	Posterior wall of left ventricle	Subendocardial fibrosis, left and right ventricles	
Strauss and Langendorf *	..	1	1	3		General fibrosis 2	General fibrosis
Yater, Cornell and Claytor *	1	2	....	2		Myocardium normal	
	2	2	0	Normal		Myocardium normal	
	3	1	....	1		Fibrosis of left ventricle and septum	
				1			
Deneke *	..	....	1	..			Diffuse fibrosis
Gaisboeck and Jurak *	..	2	4	..			Myocardial fibrosis
Biedl and Ribl *	..	....	....	..			Myocardial and endocardial fibrosis
Moenckeberg *	..	....	....	1			Septal fibrosis
Sisto *	..	3	....	2			Myocardial fibrosis
Mahaim [22]	4	3	....	..			Myocardial fibrosis
	2	....	....	..			
Gerhardt *	1	3	2	3			
	2	0	....	3			
Appelbaum and Nicolson *.	1	....	....	3	Mid part of septum		
	2	....	....	4	Anterior and posterior wall of left ventricle and septum		
Digregorio and Crawford *..	..	4	....	..		Interstitial fibrosis	
Hume *	..	L.V. 2	R.V. 1	2		Interstitial fibrosis	
Stengel *	..	L.V. 3	....	3			
Jervell *	..	1	....	4			
Cohn and Lewis [12a]	..	L.V. 1, 0	R.V. 1, 0	3			
Gertz and associates *	..	....	....	2		Moderate fibrosis	
Heninger and Dickens *	..	L.V. 3	....	3			
Menon and Rao *	..	0	L.V., R.V. 1	2			
Dreyfuss *	..	1	1	2	0	Glycogen	

* A complete reference is given in table 3A.

TABLE 4A.—*Left Bundle Branch Block: Lesions Occurring in the Upper Part of the Ventricular Septum (Data Obtained from Medical Literature)*

Author	Case	Gross Lesions	Microscopic Lesions			Clinical Observations
			Stem	Right Branch	Left Branch	
Eppinger and Stoerck [12]	1	.....	.....	Severance of branch	Intact	Congestive failure
	2	.....	.....	Fibrosis	Intact	Hypertensive cardiovascular disease
Levy, R. L., and Von Glahn, W. C.: Am. Heart J. 28: 714, 1944	8	Patches of necrosis	.....	Necrosis	Necrosis	.....
	9	Scars	.....	None	None	.....
	10	Scars	.....	.....	.....	.....
Yater [23]	4	Slight fibrosis	Normal	Moderate fibrosis	Extensive fibrosis	Partial block
	5	.....	Moderate fibrosis	Moderate fibrosis	Serious degeneration caused by fibrous tissue	.....
	6	Small scars	Moderate fibrosis	Moderate fibrosis	Moderate fibrosis; branch embedded in fibrous tissue	.....
Hill [20]	1	.....	.....	Cellular infiltration	No lesions	.....
	2	Diffuse fibrosis fibrosis	No lesion	Focus of round cell infiltration	.....	.....
Oppenheimer, B. S., and Oppenheimer, E. T.: Tr. A. Am. Physicians 45: 427, 1930	1	.....	.....	No lesion	Almost complete lesion *	.....
	2	.....	.....	Normal	Partial lesion	.....
	3	.....	.....	Normal	Partial lesion	.....
	4	.....	.....	Normal	Complete lesion	.....
	5	.....	.....	Partial lesion	Complete lesion	.....
Mahaim [22]	5	.....	.....	Complete interruption	Partial lesion	.....
	6	Infarct and aneurysm	.....	Double interruption	Partial lesion	.....
	7	Infarct and aneurysm	.....	Interruption	Partial interruption	.....
	8	.....	Partial lesion *	Complete interruption	Partial lesion	.....
	9	Infarcts	Partial interruption	Multiple interruption	"Did not escape"	.....
	10	.....	Present	Complete interruption	Interruption of posterior limb	.....
Cohn and Lewis [13a] ...	44	Patches of fibrosis	No lesion interfering with continuity			.....
	73	Fibrosis	Practically normal			.....
	91	.....	Normal	Blood sinuses	Atrophy of fibers	.....

* "Partial lesion" means a lesion in part of branch or stem; "complete lesion," complete interruption.

serial section because the fasciculus is an entity above the base of the valve and for a short distance below it. There it, too, becomes overlaid by fasciculi extending down the septum from other localities in the central fibrous ring, and as it courses toward the papillary muscle it gives off strands that disappear into the depth of the septum. The

TABLE 4B.—*Left Bundle Branch Block: Lesions Occurring Elsewhere in the Ventricles (Data Obtained from Medical Literature)*

Author	Case	Hypertrophy	Dilatation	Coronary Athero-sclerosis	Infarcts	Other Lesions
Eppinger and Stoerck [12]	1	L.V. 2, R.V. 2	.....	.....	.....	Septal fibrosis
	2	L.V. 2, R.V. 2	L.V. 3	.....	Anterior wall of left ventricle	.....
Levy and Von Glahn *	8	L.V. 2, R.V. 2	.....	Few atheromas	.....	Scars of septum and left ventricle
	9	L.V. 3, R.V. 3	3	0	0	Scars
	10	L.V. 2, R.V. 2	L.V. 4, R.V. 2	0	.....	Scars
Yater [23].....	4	L.V. 2	.....	2	.....	Slight fibrosis of myocardium
	5	3	L.V. 3, R.V. 3	L. 4, R. 2	Apex	.....
	6	3	L.V. 3, R.V. 3	1	0	Scars
Hill [20].....	1	.....	.....	.....	.....	.....
	2	.....	3	2	.....	Diffuse fibrosis
Oppenheimer and Oppenheimer *	1	.....	.....	.....	.....	.....
	2	.....	.....	.....	.....	.....
	3	.....	.....	.....	.....	.....
	3	.....	.....	.....	.....	.....
	4	.....	.....	.....	.....	.....
	5	.....	.....	.....	.....	.....
Mahaim [22].....	5	L.V. 4	L.V. 4	.....	.....	.....
	6	4	L.V. 1	4	Anterior wall of left ventricle	.....
	7	.....	.....	2	Left ventricle	.....
	8	L.V. 4	.....	.....	.....	.....
	9	.....	.....	3	.....	.....
	10	.....	.....	.....	Posterior wall of left ventricle	.....
Cohn and Lewis [13a]	44	4	.....	3	.....	.....
	73	3	.....	3 or 4	.....	.....
	91	3	.....	0	.....	.....

*A complete reference is given in table 4A.

remaining few strands become a part of the muscle fibers that form the papillary muscle. 3. Because of these anatomic peculiarities we call the strands of the myocardium, designated the right and the left branch of the His bundle, branch strips. It is impossible to have a nonexistent left branch interrupted or to describe destruction of the ridge fasciculus except with respect to its upper half; therefore, the lesions that have been described by others as totally or partially inter-

rupting the right or the left branch of the bundle of His we consider lesions occurring in the right or the left bundle branch strip. In the 7 cases which we have studied, the strips were rarely involved except when the entire upper part of the septum was maximally affected. We

TABLE 4A.—*Left Bundle Branch Block: Lesions Occurring in the Upper Part of the Ventricular Septum (Data Obtained from Our Own Cases)*

Case	Clinical Diagnosis	Gross Lesions	Replacement Fibrosis	Perivascular Connective Tissue	Other Lesions
136 x	Hypertensive cardiovascular disease	0	4	1	Thickening of walls of blood vessels
4 x	Aortic stenosis	0	4	1	Thickening of walls of many arteries
131 x	Aortic stenosis	0	L.V. 4 R.V. 3	0	Pericarditis, endocarditis
144 x	Hypertensive cardiovascular disease	0	L.V. 4 R.V. 2	1	Thickening of endocardium
2 x	Cerebral hemorrhage	0	L.V. 4 R.V. 4	0	Thickening of walls of many arteries
118 x	Coronary heart disease; QRS, 0.11 second	Infaret	2	3	Endocarditis
102 x	Rheumatic disease, aortic stenosis; QRS, 0.10 second; left ventricular strain	0	2-3	2	Thickening of walls of few blood vessels, thickening of endocardium

TABLE 4D.—*Left Bundle Branch Block: Lesions Occurring Elsewhere in the Ventricles (Data Obtained from Our Own Cases)*

Case	Hypertrophy	Dilatation	Coronary Atherosclerosis	Infarcts	Other Lesions
136 x	L.V. 4, R.V. 3	L.V. 1, R.V. 1	1	0	Replacement fibrosis 2
4 x	L.V. 4, R.V. 1	L.V. 2, R.V. 2	2-3	0	Replacement fibrosis 2; perivascular fibrosis
131 x	L.V. 3, R.V. 2	L.V. 2, R.V. 2	1	0	Replacement fibrosis 1-2; pericarditis
144 x	L.V. 4, R.V. 4	L.V. 3, R.V. 3	2-4	Posterior base, small	Replacement fibrosis 3
2 x	L.V. 0, R.V. 0	L.V. 2, R.V. 1	0	0	Replacement fibrosis 3
118 x	L.V. 3, R.V. 2	L.V. 2, R.V. 2	4	Anterior 1, posterior 1, both involving septum	Perivascular fibrosis 3
102 x	L.V. 3, R.V. 3	L.V. 2, R.V. 2	1	0	Thickening of endocardium

have grouped the cases of table 4 *A* with those of 4 *C*, making a total of 31 cases.

In 25 of these the morbid changes were sufficiently extensive to have brought about bundle branch block; in 6, no such lesions existed. Among the 24 cases from the literature were 18 in which information concerning lesions elsewhere in the ventricle was given. This information together with that of our own 7 cases is now analyzed: The left ventricle was moderately to maximally enlarged in 20; the right, mod-

erately to maximally in 16. One of the hearts was normal in size; another, only slightly enlarged. Dilatation of the left ventricle was recorded for 16 hearts and was moderate to maximal in all but 3. Dilatation of the right ventricle was noted in 10 cases; it was minimal in 2 cases and moderate to marked in the others. The condition of

TABLE 5A.—*Right Bundle Branch Block: Lesions Occurring in the Upper Part of the Ventricular Septum (Data Obtained from Medical Literature)*

Author	Case	Gross Lesions	Microscopic Lesions			Clinical Observations
			Stem	Right Branch	Left Branch	
Meessen, H.: Ztschr. f. Kreislaufforsch. 27: 42, 1935	..	.....	Passive congestion	Normal	Myeloid infiltration	.....
Crawford, J. H., and DeVeer, J. A.: Am. Heart J. 7: 780, 1932	..	Aneurysm	Conduction pathway could not be identified because of fibrosis			Heart block
Starling, H. J., and DeNavasquez, S.: Guy's Hosp. Rep. 88: 240, 1938	..	Necrosis and fibrosis	Branches disappeared in fibrous tissue			Heart block
Master, A. M.; Dack, S., and Jaffe, H. L.: Am. Heart J. 16: 283, 1938	14	Infarct involving entire septum	.....	.....	.....	.....
	40	Infarct involving entire septum	.....	.....	.....	.....
Yater [22]	1	Small scars	Fibrosis	Destroyed by scar	Interstitial connective tissue increased	Rheumatic heart disease
	2	Scars, right	Slight degeneration	Practically complete fibrous replacement	Some fibrosis	Rheumatic heart disease
	3	Much scarring	50% fibrotic	Complete fibrous replacement	Some fibrosis	Rheumatic heart disease, heart block
Braunstein, A. L.; Bass, J. B., and Thomas, S.: Am. Heart J. 19: 283, 1938	..	Aneurysm and necrosis	Extensively destroyed by syphilitic process			Heart block
Taussig [19]	..	Irregular patches of fibrosis	.....	.....	Complete break in continuity	.....
Oppenheimer and Pardee [18]	..	.....	.....	Complete destruction	Normal	.....
Mahaim [22]	14	.....	Present	Present	Present	.....

the coronary arteries was noted in 19 cases. The extent of atherosclerosis varied from 0 to grade 2 in 13 cases and was grade 3 or 4 in 6 cases. Infarcts involving the lower part of the septum were found in 6 cases. It therefore appears that the lesions found outside the septum had little or no effect on the bundle branch block.

Right Bundle Branch Block.—Tables 5 A, 5 B, 5 C and 5 D contain information about the morbid anatomy observed in 17 cases of right bundle branch block, 12 from the literature and 5 of our own. Among

TABLE 5B.—*Right Bundle Branch Block: Lesions Occurring Elsewhere in the Ventricles (Data Obtained from Medical Literature)*

Author	Case	Gross Lesions: Hypertrophy	Dilatation	Coronary Atherosclerosis	Infarcts	Other Lesions
Meessen *	..	L.V. 2	.....	None	.....	.....
Crawford and DeVeer *	..	4	.....	2	.....	.....
Starling and DeNavasquez *	..	L.V. 4	R.V. dilated	2 2	.....	.....
Master *	14	.....	.....	4 4	.....	.....
	40	3	.....	4 4	.....	.....
Yater [28]	1	L.V. 1 R.V. 2	R.V. dilated	..	.....	Mitral stenosis
	2	L.V. 0 R.V. 2	L.V. not much dilated	1	.....	Mitral and aortic stenosis
	3	L.V. 1 R.V. 2	0	0	.....	.....
Braunstein and associates *	..	2	R.V. 4	All vessels patent	.....	.....
Taussig [19]	..	L.V. 0 R.V. 4	.....	0	.....	Mitral stenosis

* A complete reference is given in table 5A.

TABLE 5C.—*Right Bundle Branch Block: Lesions Occurring in the Upper Part of the Ventricular Septum (Data Obtained from Our Own Cases)*

Case	Clinical Diagnosis	Gross Lesions	Replacement Fibrosis	Perivascular Connective Tissue	Other Lesions
1 x	Chronic rheumatic heart disease, mitral stenosis	0	0	L, 1-2, R, 3-4	Aschoff bodies
117 x	.....	0	L, 1, R, 2-3	1	Thickening of walls of blood vessels
130 x	Carcinoma of pancreas, "S type"; QRS 0.16 seconds	0	L, 2-3, R, 2-3	0	Thickening of walls of blood vessels
111 x	Cirrhosis, "S type"	0	0	1	0
114 x	Coronary heart disease, "S type"	0	0	1	0

TABLE 5D.—*Right Bundle Branch Block: Lesions Occurring Elsewhere in the Ventricles (Data Obtained from Our Own Cases)*

Case	Hypertrophy	Dilatation	Coronary Atherosclerosis	Infarcts	Other Lesions
1 x	L.V. 1, R.V. 4	L.V. 1, R.V. 4	0	0	Areas of round cell infiltration; perivascular fibrosis
117 x	L.V. 2, R.V. 2	L.V. 1, R.V. 4	1-2	0	Perivascular sclerosis, 1
130 x	L.V. 3, R.V. 2	L.V. 2, R.V. 2	2-3	Small, in lateral wall of left ventricle	Perivascular fibrosis
111 x	L.V. 0, R.V. 0	L.V. 1, R.V. 2	1	0	Perivascular fibrosis, 1
114 x	L.V. 0, R.V. 2	L.V. 0, R.V. 0	4	Posterior wall, near apex	Perivascular fibrosis, 2

the cases from the literature gross lesions occurred in the upper part of the ventricular septum in 9; the lesions were stated to have destroyed both branches of the His bundle in 3. The stem and the branches had been examined in serial sections in 7 cases: The right branch was completely interrupted in 4; fibrosis was present within the branch in 1; the branch was normal in 1. There was complete break of continuity in the left branch of the His bundle in 2 cases; some fibrosis was found in 3; the branch was normal in 1. Two of our 5 cases of right bundle branch block were of the classic type. One of the hearts was free from replacement fibrosis but had rather marked rheumatic changes in both ventricles; the other showed moderate replacement fibrosis on the right side, minimal on the left. Three of the 5 cases were of the S type of right bundle branch block. One of the hearts had grade 3 replacement fibrosis on both sides of the septum; 2 had neither gross nor microscopic lesions. To summarize, in 14 of the 17 cases lesions were observed which might be etiologically related to bundle branch block.

Information about hypertrophy and dilatation of the hearts is given in 10 of the cases from the literature and in our own: The left ventricle was normal or only slightly hypertrophied (grade 2) in 10; the right, in 7. Maximal hypertrophy was present on the right side in 3 cases; maximal dilatation, in 3 of 11 cases. Atherosclerosis of the coronary arteries was absent to moderate in 11 cases, maximal in 3. Two infarcts were found, a small one in the lateral wall of the left ventricle and a posterior one near the apex.

It has already been pointed out that attempts made by others to find the causal lesion of right or left bundle branch block in the side of the septum where the electrocardiographic pattern indicated its presence led to confusion. The information obtained by us is not much more illuminating so far as locating the block is concerned. In only 1 case of typical right bundle branch block was there decidedly more inflammatory involvement in the right than in the left ventricle. In another case the replacement fibrosis of the upper part of the ventricular septum was moderate on the right, minimal on the left. In our 5 cases of typical left bundle branch block the replacement fibrosis was maximal on the left side; however, in 3 it was also maximal on the right. In the remaining 2 cases it was moderate in one and marked in the other, on the right side. It appears, therefore, that the predominance of lesions in one or the other side of the septum may, in a small percentage of cases, lead to the corresponding bundle branch block. However, the factor that usually determines the electrocardiographic pattern is the type of preponderance curve existing prior to the prolongation of the QRS

interval. This concept is suggested also from the observations of Hyman,[39] Luten,[40] Barnes[41] and their collaborators.

Indeterminate Block.—Tables 6 A and 6 B record the essential findings in 11 cases recorded in the literature; tables 6 C and 6 D give our own observations in 8 cases. Gross lesions were found in the septum in 8 of the cases collected from the literature; in 7 they were infarcts, and in the remaining case a syphilitic aneurysm involved the sinus of Valsalva. In 9 of the cases from the literature the causal lesions were sought in the right and left branches: In 1 the right branch was seen and lost, and the left was not recognized; in 1 noninterrupting lesions were found; in 1 necrosis had destroyed both branches. In 6 cases special search had evidently been made for lesions in both branches. In 5 the left branch had been completely interrupted and in 1 incompletely destroyed. In 1 the right branch had been interrupted, in 1 it had been partially interrupted, and in 4 it was normal.

In our own cases we found moderate to marked replacement fibrosis on the left side of the septum in 2, moderate to marked on the right side in 1, minimal on both sides in 3, none in 2, and minimal on the right side in 1 case in which the replacement fibrosis was moderate on the left. In cases 105x and 140x the infarcts extended far enough to involve the left branch strips. The infarcts of the upper part of the septum were small and did not involve its entire upper edge. In 1 case two small infarcts were present on the right side of the septum below the septum membranaceum; in 3 cases the infarcts involved only the left side of the septum.

In the 6 cases from the literature in which the state of hypertrophy and dilatation was recorded, it was minimal in 1 and moderate to marked in 5. In our own 8 cases hypertrophy was minimal on the left side in 3 and on the right side in all but 1; in the other cases it was moderate to marked on the left, in 1 of which it was also moderate on the right. We observed dilatation on the left in 8 cases, marked in 2 and minimal in 6; we observed it on the right in 8 cases, moderate to marked in 4 and minimal in 4. Atherosclerosis of the coronary arteries was maximal in 4 of the recorded cases and in 7 of our own. Elsewhere in the ventricles only one infarct was observed in the cases recorded in the literature, but seven infarcts were found in our own cases. It therefore appears that among the 19 cases of indeterminate block analyzed, there were 13 with lesions in the upper part of the septum that might have been responsible for the defect of conduction. However, in 6 cases such lesions were not found.

39. Hyman, A. S., and Parsonnet, A. E.: Arch. Int. Med. **45**:868, 1930.

40. Luten, D., and Grove, E.: Am. Heart J. **4**:431, 1929.

41. Barnes, A. R., and Whitten, M. B.: Am. Heart J. **5**:14, 1929.

TABLE 6A.—*Indeterminate Block: Lesions Occurring in the Upper Part of the Ventricular Septum (Data Obtained from Medical Literature)*

Author	Case	Gross Lesions	Microscopic Lesions: Stem	Microscopic Lesions: Right Branch	Microscopic Lesions: Left Branch	Clinical Observations
Meessen, H.: Ztschr. f. Kreislaufforsch. 27 : 42, 1935	..	.....	Noninterrupting lesions			.....
Oppenheimer and Rothschild [16]	8	.....	.....	.....	.....	.....
Levy, R. L., and Von Glahn, W. C.: Am. Heart J. 28 : 714, 1944	7	Necrosis	"Necrosis extending to bundle branches"			.....
Rosenthal, S. R.: Arch. Int. Med. 50 : 730, 1932	..	Aneurysm of right sinus of Valsalva	.....	Not interrupted	Interrupted	Syphilis
Master, A. M.; Dack, S., and Jaffe, H. L.: Am. Heart J. 16 : 283, 1938	9	Infarct involving entire septum	.....	.....	.....	.....
Oppenheimer, B. S., and Oppenheimer, E. T.: Tr. A. Am. Physicians 45 : 427, 1930	6	.....	.....	Normal	Completely destroyed	.....
	7	.....	.....	Normal	Completely destroyed	.....
	8	.....	.....	Normal	Completely destroyed	.....
	9	.....	.....	Normal	Incompletely destroyed	.....
Mahaim [22]	2	.....	.....	Interrupted	Interrupted	.....
Cohn and Lewis [10a]	42	.....	Normal	Branch seen and lost	Not recognized	.....

TABLE 6B.—*Indeterminate Block: Lesions Occurring Elsewhere in the Ventricles (Data Obtained from Medical Literature)*

Author	Case	Gross Lesions: Hypertrophy	Gross Lesions: Dilatation	Gross Lesions: Coronary Atherosclerosis	Gross Lesions: Infarcts	Gross Lesions: Other Lesions
Meessen *	..	2	R.V. 2	L. 4, R. 2	Aneurysm involving lower part of septum	Marked fibrosis involving left Purkinje network
Oppenheimer and Rothschild [16]	8	..	..	3 to 4	.....	"Sclerosis predominates in endo- and subendocardium, more marked in left than in right ventricle" *
Levy and Von Glahn *	7	3	3	1	.....	Scars in left ventricle
Rosenthal *	..	2	..	1	.....	.....
Master *	9	Cardiac enlargement	..	4	.....	.....
	46	1	..	4	.....	.....
Oppenheimer and Oppenheimer *	6	..	..	..	.....	.....
	7	..	..	..	.....	.....
	8	..	..	..	.....	.....
	9	..	..	..	.....	.....
Mahaim [22]	2	..	..	2	.....	.....
Cohn and Lewis [10a]	42	3	..	1	.....	.....

* A complete reference is given in table 6A.

GENERAL COMMENT

The information found in tables 3 to 6 reveals the essential ventricular morbid anatomy of heart block and intraventricular block. In the 7

TABLE 6C.—*Indeterminate Block: Lesions Occurring in the Upper Part of the Ventricular Septum (Data Obtained from Our Own Cases)*

Case	Clinical Diagnosis	Gross Lesions	Replacement Fibrosis	Perivascular Connective Tissue	Other Lesions
119 x	Coronary heart disease, PR: 0.24 second, QRS: 0.12 second	Infarcts, posterior and anterior; none in middle	L.V. 2, R.V. 1	0	0
105 x	Coronary heart disease, arborization block, QRS: 0.16 second	Infarct, nearly to upper edge of septum	Infarct involving left branch strip	0	Thickening of walls of blood vessels 1
115 x	Coronary heart disease	Infarct, posterior half of septum	0	1	0
103 x	Hypertensive cardiovascular disease	0	L.V. 2-3, R.V. 2-3	0	Thickening of walls of few blood vessels
106 x	Coronary heart disease	0	1	0	0
109 x	Rheumatic heart disease, hypertensive cardiovascular disease	0	1	3	Thickening of adventitia of blood vessels
116 x	Coronary heart disease	Two small infarcts, right side of septum between edge and papillary muscle	1	0	0
140 x	Coronary heart disease	Septal infarct, left side	0	0	0

TABLE 6D.—*Indeterminate Block: Lesions Occurring Elsewhere in the Ventricles (Data Obtained from Our Own Cases)*

Case	Hypertrophy	Dilatation	Coronary Atherosclerosis	Infarcts	Other Lesions
119 x	L.V. 3, R.V. 2	L.V. 3, R.V. 2	4	Posterior involving septum	Mural thrombus
105 x	L.V. 2, R.V. 1	L.V. 3, R.V. 3	3-4	Anterior, large	0
115 x	L.V. 2, R.V. 1	L.V. 1, R.V. 1	4	Anterior and posterior, large	Perivascular fibrosis, 1
103 x	L.V. 3, R.V. 1	L.V. 1, R.V. 2	1-2	0	0
106 x	L.V. 2, R.V. 1	L.V. 1, R.V. 2	3	0	Perivascular fibrosis at base
109 x	L.V. 1, R.V. 1	L.V. 1, R.V. 1	2-3	Lateral, small	Perivascular fibrosis, 2
116 x	L.V. 1, R.V. 1	L.V. 1, R.V. 1	2-4	Posterior, not involving septum	Edema, slight
140 x	L.V. 1, R.V. 1	L.V. 1, R.V. 1	3-4	Anterior	0

control cases, only insignificant lesions were found in the upper part of the ventricular septum, whereas in 90 per cent of the recorded 28 cases of heart block the heart had extensive lesions. We believe

these lesions to be significant because a considerable portion of the septal myocardium had been destroyed. Similar lesions were found in the upper part of the septum in approximately 80 per cent of 31 cases of left bundle branch block, in 82 per cent of 18 cases of right bundle branch block and in 69 per cent of 19 cases of indeterminate block.

The morbid changes were of several types but were alike in the damage that they had inflicted on the heart muscle. The majority of the lesions were ischemic, the ischemia being caused by obstructive lesions of the ventricular arteries. When a main coronary artery was occluded (it was nearly always the right), gross infarction occurred in the upper part of the septum. When the lumens of the septal arteries were obstructed, replacement fibrosis resulted. The amount and extent of the replacement fibrosis varied from tiny patches involving only a few muscle fibers to extensive destruction of whole muscle bands (inner part of the superficial bulbospiral and the deep bulbospiral muscles—Robb [38]). Calcification was present with fibrosis in 5 of the cases of heart block. Infectious agents—those of syphilis, tuberculosis and rheumatism—were responsible for extenive lesions. Rheumatic lesions, widely distributed throughout the myocardium as scars and active inflammatory changes, were the only significant lesions found in some of the cases of right bundle branch block. When the lesions involved principally that part of the septum which lies above the lowest point of the septum membranaceum, heart block seemed to be the only conduction abnormality present. When, however, the abnormal changes extended below this level, intraventricular block was frequently present. In about 30 per cent of the cases of heart block the heart had ancillary bundle branch block.

The lesions found elsewhere in the ventricles—replacement fibrosis, hypertrophy, dilatation, marked atherosclerosis with infarct formation, and interstitial myocarditis—do not appear to have had any appreciable effect on the abnormal conduction which was present, because these changes were present in our control cases as often as in the others and were present or absent in the same ratio in all the types of block. A possible exception occurred in 2 cases of right bundle branch block with marked generalized rheumatic inflammatory changes involving the whole right ventricle.

Our study does not furnish any direct proof that the generalized lesions of the upper part of the septum are causally related to the conduction disturbances under consideration, nor do we have any method of determining whether or not the lesions described (if they are the actual cause of block) were aided by unknown factors also influencing conduction. We assert only that the damage done to the myocardium by the lesions is probably sufficient to have brought about the abnormal

conduction. Even if it be granted that the morbid changes occurring in the septum are the actual causes of the abnormal conduction, the bald fact remains that in approximately 10 per cent of cases of heart block and 20 to 30 per cent of cases of intraventricular block neither other observers nor we have found any morbid changes in the ventricles that could account for the abnormality of conduction.

At the onset of our inquiry into the genesis of the various kinds of heart block we were aware that the entire question could not be solved by our investigation of the morbid changes involving the myocardium. There are two obvious reasons for the limitations of our method: 1. It is well known that profound and even lethal disturbances of muscle function may occur without leaving alterations of structures detectable by the technic employed. It is possible that both atrioventricular dissociation and intraventricular conduction delay can be brought about by such disturbances. But the following reason is more apparent: 2. The heart possesses a well developed intrinsic nervous system far more conspicuous than the Auerbach and Meissner plexuses of the intestine. Modern anatomists appear to be but dimly aware of the existence of this system, and modern physiologists seem hazy about its function. This state of affairs exists in spite of the fact that Stannius [42] long ago showed that a ligature applied to the frog's ventricles below the part where nerve cells are present causes stoppage of the apical myocardium; and Carlson [43] decades ago showed that contraction of the entire ventricle of the heart of the limulus, or that part of the heart which was deprived of its intrinsic nerve supply, stops the beating permanently. We maintain that it is physiologically sound to assume that the heart beat originates in some of the numerous ganglions found in the atriums, that the synchronism of the contractions of the atriums and the ventricles is a function of these nerve cells and that the ventricles as well as the atriums are activated by impulses carried in the axis-cylinders of the atrial nerve cells; furthermore, that cardiac conduction, normal or abnormal, is more or less influenced by the intrinsic nervous system of the heart and that, therefore, this system exerts an influence in all disturbances of conduction and may play a stellar role in such cases of heart block as that repeatedly reported on by Coffen [44] and in such temporary bundle branch block as that observed recently by Graybiel and his collaborators.[45]

42. Stannius, D.: Arch. f. Anat., Physiol. u. wissensch. Med. **18**:85, 1852.

43. Carlson, A. J.: Ergebn. d. Physiol. **8**:371, 1909.

44. Coffen, T. H.; Rush, H. P., and Miller, R. F.: Northwest Med. **40**:195, 1941.

45. Graybiel, A.; McFarland, R. A.; Gates, D., and Webster, F. A.: Am. Heart J. **27**:524, 1944.

Obviously, the intrinsic nervous system of the heart undergoes morbid changes like those of other tissues. Yet we are not aware of any one who has even attempted to study the morbid anatomy of this system. It, therefore, appears that our present concept of cardiac conduction in health and in disease is comparable to the concept of the circulation of the blood which was held by the profession in the pre-harveian day.

SUMMARY

Since this disquisition is the last of a series on the morphology of the cardiac conduction system, a general summary of our observations follows:

1. A sinoatrial node does not exist in the sulcus terminalis of man, dog, rhesus monkey, swine, sheep, cattle or horse.

2. Nor did we find in the hearts of the same species a special atrioventricular muscle conduction bundle.

3. However, in sheep, cattle, swine and horse there is present a distinct ventricular bundle composed of about half nerve tissue and half altered muscle fibers. This bundle begins in the atrioventricular fibrous ring, has a stem, a right and a left branch, and terminates in a subendocardial and an intramyocardial network.

4. No structure analogous to this bundle exists in the ventricle of man, dog or rhesus monkey.

5. The bundle described by His appears to have been a group of ordinary muscle fasciculi of the left side of the septum, originating in the central atrioventricular fibrous ring, and spreading out over the septum as the fasciculi run toward the apex.

6. There is no atrioventricular node in the heart of man, dog or rhesus monkey.

7. The structure which has been described as the stem of the His bundle of man is the supervalvular part of an ordinary muscle fasciculus —the ridge fasciculus. The right branch of the His bundle is the infravalvular part of this ridge fasciculus. The fasciculus does not give off a left branch.

8. Experimental investigators who have assumed that a distinct Flack-Tawara conduction system exists in experimental animals and in man have attempted to demonstrate its function by experimental attack:

(*a*) Ablation experiments on the "node of Keith and Flack" have failed to demonstrate a special function of the node.

(*b*) Incision of the left side of the septal myocardium to sever the left branch of the His bundle or clamping of the upper edge of the interventricular septum to compress the stem of

the His bundle produced heart block, and incisions of the right and left myocardium to sever the right and left branches of the His bundle produced bundle branch block in experimental animals and in man. These results were interpreted as due solely to the injury done to the His bundle or its branches. No cognizance was given to the extensive damage produced in the septal myocardium.

9. Other investigators who also took for granted that a morphologically distinct conduction system exists in man have found the causal lesions of heart block in the stem and the branches of the His bundle and the causal lesions of bundle branch block in one or the other of the branches of this bundle. But an evaluation of the lesions found in terms of the conduction defects revealed by the electrocardiograph leads to confusion rather than clarity (tables 3 to 6), because a His-Tawara bundle does not exist in the human heart.

10. However, experimental injury done to the upper part of the ventricular septum in animals and man does bring about heart block and bundle branch block, and more or less extensive lesions have been found in the upper part of the ventricular septum of man in heart block and bundle branch block. In the present communication we have analyzed the observations made by others in 76 cases of conduction disturbances and have added them to our observations of 28 human hearts, with the following results:

(*a*) In approximately 90 per cent of cases of heart block the myocardium of the upper part of the septum had been extensively injured by various kinds of lesions. Similar lesions were found in 70 to 80 per cent of cases of the various types of bundle branch block. It is our opinion that the lesions reported had produced sufficient damage of this part of the myocardium to account for the conduction disturbances which had been present during life.

(*b*) In the remainder no significant lesions were found.

11. The lesions observed in the ventricles of the examined hearts in places other than the upper part of the interventricular septum do not appear to be causally related to the conduction disturbances in the cases which form the basis of this communication.

12. We postulate that in the cases of heart block and bundle branch block in which the upper part of the septum appeared practically unchanged, the "clinical blocks" which were present might have been due to:

(*a*) morbid physiologic changes not detectable by our methods or

(*b*) lesions of the intrinsic nervous system of the heart.

CONCLUSIONS

1. From our morphologic study of the localities where the special conduction system of the heart is supposed to be we conclude that an atrioventricular muscular conduction system does not exist in any of the species studied. Therefore, the present concept of cardiac conduction is as inaccurate as was the concept of the circulation in preharveian days.

2. In from 70 to 90 per cent of clinical atrioventricular and intraventricular blocks extensive lesions are found in the myocardium of the interventricular septum. These lesions probably bear a causal relation to the "blocks."

MANIFOLD MANIFESTATIONS OF RETICULO-ENDOTHELIAL DISEASE

Report of a Case of Hodgkin's Disease (Lymphogranulomatosis), Acute Hemolytic Anemia and Giant Follicular Lymphadenopathy

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HEMOLYTIC crises occurring in association with Hodgkin's disease, lymphosarcoma or lymphatic leukemia are well known and are referred to under the heading of "symptomatic hemolytic anemia."[1]

In Watson's[2] series of 35 cases of leukemia and Hodgkin's disease were 3 in which the patients had associated hemolytic anemia. Of the 9 cases of microcytic hemolytic anemia described by Davidson,[3] Hodgkin's disease was present in 3; yet the association of the two conditions must be rare, as shown by the absence of any mention of hemolytic episodes in the series of 618 cases of lymphoma of Gall and Mallory,[4] including cases of lymphoblastic, lymphocytic, plasmacytic, follicular and stem cell lymphoma, Hodgkin's lymphoma and Hodgkin's sarcoma.

Is the association of the two pathologic conditions a casual coincidence, or are they interrelated, in the sense that one condition might bring about the other, or are they independent manifestations of a general disorder of the reticuloendothelial system expressing itself in different fashions?

A case came to our observation in which there was shown in succession a cervical granuloma diagnosed as Hodgkin's disease, the typical picture of acute hemolytic anemia and later mixed types of lymphadenopathy with combined patterns of giant follicular lymphadenopathy and Hodgkin's disease. This unusual coincidence of pathologic conditions seemed worthy of note.

From the Division of Laboratories and the Medical Service of the Framingham Union Hospital.

This investigation was aided by the Lydia Raymond Publications and Research Fund of the Framingham Union Hospital

1. Dameshek, W., and Schwartz, S. O.: Am. J. M. Sc. **179**:228, 1930.
2. Watson, C. J.: Ann. Int. Med. **12**:1782, 1939.
3. Davidson, L. S. P.: Quart. J. Med. **25**:543, 1932.
4. Gall, E. A., and Mallory, T. B.: Am. J. Path. **18**:381, 1942.

REPORT OF CASE

First Admission (Cervical Hodgkin's Disease).—A 34 year old white man, single, an American, with irrelative past and familial history, was admitted to the Massachusetts General Hospital in July 1935 for study because of a mass which had been present on the right side of his neck for three months. The mass was excised and presented the typical picture of Hodgkin's disease.

The microscopic sections showed obliteration of the usual lymph node structure, due to a disorderly proliferation of cells, which varied greatly in size and arrangement. The most striking cell type was represented by large cells, with irregular outlines, which ranged from 10 to 30 microns in diameter. The cytoplasm of these cells was abundant and compact and displayed marked acidophilia. At times these cells showed single nuclei, round, oval or slightly indented, and vesicular, with abundant, scattered chromatin. At other times these cells showed several nuclei, dissimilar in size and shape, clustered in the center of the cell and connected by narrow bridges (Reed-Sternberg giant cell). Unipolar and, less frequently, multipolar mitotic figures and an abundance of a great variety of other elements were present besides the giant cells (fig. 1). Lymphocytes and plasma cells were predominant, but quite numerous granulocytes (both eosinophilic and neutrophilic), monocytes and histiocytes were also present. Focal necrosis was noted in places, and around these areas phagocytes were numerous. There was rather abundant production of collagen and wavy connective tissue fibers gave rise at many points to a thick network, in the meshes of which lay the proliferating mesenchymal cells. Elsewhere the connective tissue fibers showed a tendency to fuse in broad septums which separated the cellular foci into islands. There was pronounced hyperplasia of the cells lining the sinuses. The blood vessels, both small and middle sized, showed thickening of their walls, at times also hyperplasia of their lining cells. The fibrous capsule was free from cellular infiltration except for a few foci of lymphocytes which were present here and there.

Following the pathologic report, a course of roentgen irradiation of the neck was administered. Complete studies of the blood gave negative results.

Second Admission (Acute Hemolytic Anemia).—The patient was admitted to the Framingham Union Hospital, Sept. 26, 1940, with a chief complaint of fatigue and headache of one month's duration. His fatigue was progressive, and, in addition, jaundice was noted by a nurse at the factory where he was employed. He was then referred to his family physician, who felt that he might have catarrhal jaundice and prescribed "rest in bed." However, his condition did not improve, and hospitalization was advised. Examination revealed a well developed and well nourished white man complaining of severe headaches, weakness and general abdominal soreness. He was extremely pale and had a slight icteric tinge of the skin and the conjunctiva, but otherwise examination failed to reveal any deviation from the normal. His temperature was 99 F.; the pulse rate was 100 and the respirations 20. The blood pressure was 140 mm. of mercury systolic and 90 mm. diastolic. The red blood cell count was 2,300,000; the hemoglobin content, 43 per cent; the reticulocyte count, 19.2 per cent. The white cell count was 19,100; the differential count showed 63 per cent segmented cells, 8 per cent unsegmented ones, 26 per cent lymphocytes and 3 per cent monocytes. The blood smear revealed marked polychromatism and anisocytosis with a tendency toward spherocytosis; the fragility of the red cells was 0.6 to 0.4, with control 0.4 to 0.35; the icteric index was 33. The urine revealed increased urobilinogen. The stool tested for occult blood was negative. During the first nine days of hospitalization the patient

showed a gradually downward trend in the condition of his blood. A diagnosis of acute hemolytic anemia was made and repeated blood transfusions were given, but they resulted in only temporary improvement. October 5, the patient had an acute hemolytic crisis, the number of red cells dropping to 1,100,000 per cubic millimeter and the hemoglobin concentration to 27 per cent. After an initial chill he was given two transfusions of 500 cc. of whole blood, both of which resulted in subsequent chills and hemoglobinuria. On the same day the patient underwent splenectomy (Dr. Eugene A. Gaston), preceded and followed by more blood transfusions.

The spleen measured 15 by 10 by 5 cm. and weighed 360 Gm. Its contour was regular, and the capsule was smooth, glistening and slate gray. On the cut section the pulp was increased and was deep crimson. No lymph follicles were seen, and the trabeculae did not appear to be thickened.

Microscopic sections showed complete obliteration of the usual structure. The limits between the pulp and the follicles were not clearly made out, and the latter appeared to be greatly diminished both in size and in number. This was due mainly to extreme congestion of the pulp. The sinusoids were engorged, and red blood cells infiltrated the pulp. Only a few of the red blood cells were well preserved; the majority appeared as "shadows" fused together in blocks of homogeneous glassy eosinophilic material with almost complete loss of cellular outlines. Another striking finding was marked proliferation of reticulum cells, the new cells appearing either singly or in clumps, accompanied by widespread erythrophagocytosis. Groups of myeloblasts, myelocytes and occasional erythroblasts could be recognized in places and were interpreted as foci of ectopic myeloid metaplasia (fig. 2). Cells identical in type were occasionally seen in malpighian follicles, which still displayed active germinal centers. Elsewhere the follicles showed blocks of amorphous eosinophilic material, which did not stain metachromatically and was interpreted as an evidence of hyaline change (fig. 3). This hyaline change seemed to be preceded by hyperplasia of young mesenchymal cells and fibroblasts. There was hyalinosis of the follicular arteries leading to narrowing and complete obliteration. Both capsule and trabeculae were thickened, owing to proliferation of connective tissue fibers and to edematous swelling. The increase of collagenous tissue was accompanied in some areas by increased cellularity. The majority of these cells were fibroblasts and histiocytes, but numerous granulocytes of the eosinophilic type, either sparse or in small groups, were seen also—most frequently beneath the fibrous capsule and in the proximity of the trabeculae.

The diagnosis was "hemolytic spleen," emphasizing the extensive erythrophagocytosis and hyperplasia of reticulum cells. The foci of myeloid metaplasia were interpreted as compensatory to the severe blood dyscrasia, whereas the increase of collagenous tissue and the hyalinosis of the lymph follicles were thought to be regressive changes resulting from the limitation of the blood supply.

The postoperative course was good. There was a slow but steady improvement of the blood, so that one week after the operation the red cell count was increased to 2,180,000 and the hemoglobin content to 42 per cent. The headaches and other symptoms were markedly relieved. On the nineteenth postoperative day, a sudden sharp pain developed in the lower part of the left side of the chest, accompanied by sweating, pallor and dyspnea and followed by fever. There was limited expansion, with muffled breath sounds and moist rales at the base of the lower lobe of the left lung posteriorly. Roentgenograms showed increased density and it was felt that the patient had a small pulmonary infarction. Several days later he was gaining progressively in strength, and was discharged Nov. 6, 1940, the thirty-second postoperative day, in excellent condition.

Third Admission (Cervical Giant Follicular Lymphadenopathy and Hodgkin's Disease).—The patient was readmitted, June 21, 1942, because of an enlarged lymph node in the left side of his neck, which had developed gradually over a period of about six weeks, without any general discomfort. After his discharge, in 1940, he felt perfectly well, and the red blood cells and the hemoglobin returned to normal. At this, his third, admission examination gave essentially negative results except for a firm but not tender mass at the angle of the jaw on the left side, measuring about 5 cm. in the largest dimension. The blood showed 4,180,000 red cells, a hemoglobin content of 95 per cent, and 15,800 white cells, of which 76 per cent were segmented cells, 3 per cent unsegmented cells, 19 per cent lymphocytes

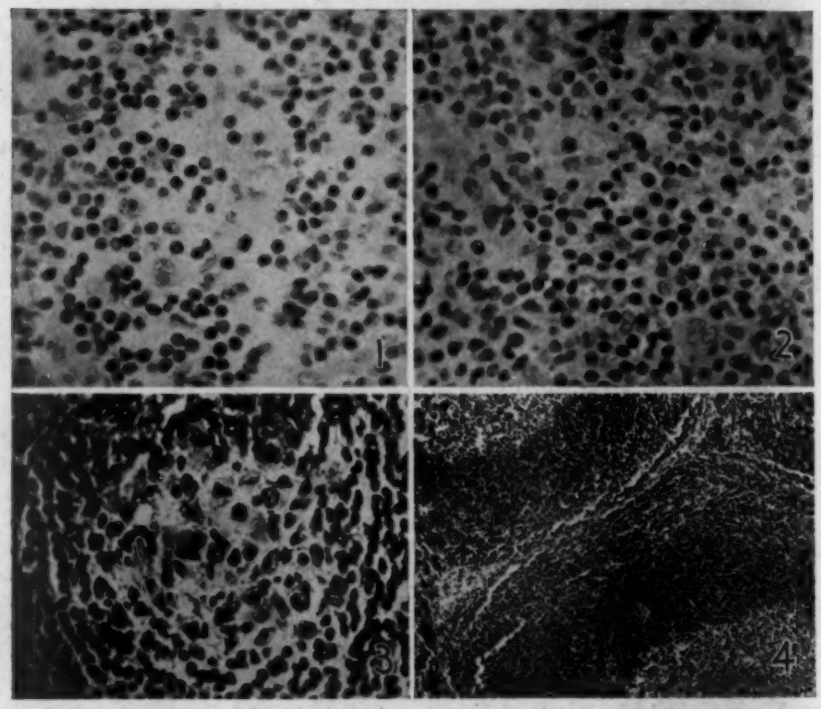

Fig. 1.—Section of the cervical mass removed in 1935, showing the usual lymph node structure replaced by infiltrating giant cells of the Reed-Sternberg type, irregularly intermixed with lymphocytes, plasma cells and a variety of other mesenchymal cells; Zeiss, ocular 10, objective 40. This slide was lent by the Department of Pathology, Massachusetts General Hospital, Boston.

Fig. 2.—Part of a focus of splenic myeloid metaplasia; Zeiss, ocular 7, objective 40.

Fig. 3.—Center of follicular hyalinization, with hyperplasia of young mesenchymal cells in the spleen; Zeiss, ocular 5, objective 40.

Fig. 4.—Lymph follicle giantism; from an area of the cervical mass removed in 1942; Zeiss, ocular 5, objective 40.

and 2 per cent eosinophils. A fragility test was normal. Under ether anesthesia, the cervical mass was removed. The specimen consisted of a moderately firm, grayish pink mass which measured 4 by 2.5 by 2.3 cm. On the cut section it

appeared to be a conglomerate of lymph nodes, smooth and grayish pink externally and juicy on the cut surfaces.

The cellular pleomorphism and the Reed-Sternberg type of giant cells which in 1935 had led to the diagnosis of Hodgkin's disease were present in the cervical lymph nodes now removed, but in limited areas and not so strikingly. The striking feature at this time was multiple follicle-like nodules of varied size and approximation, the majority of which had reached gigantic proportions (fig. 4). These follicle-like nodules showed huge germinative centers of loosely packed masses of large lymphocytic cells, with intimate cytologic characteristics of lymphoblasts. Among these cells a delicate reticulum could be seen, and about each germinative center there was a thick mantle of mature, small lymphocytes. Each follicle was sharply limited, and between follicle and follicle was a thin rim of compressed lymphoid tissue. In many places, however, the follicles appeared to have broken through the internodular tissue, to become confluent, with complete obliteration of the normal structure, and compression and disappearance of sinus spaces, simulating lymphocytic lymphoma. Mitotic figures could be recognized but occurred only occasionally. The fibrous capsule was thickened, owing mostly to proliferation of collagen, and only in limited areas were there any infiltrating cells, mostly lymphocytes. It deserves mention that there was a considerable amount of yellowish brown granules of blood pigment throughout the tissue. Some of the granules were free, while others were within large macrophages. The largest deposits of pigment were in the endothelial cells lining the sinuses, many of which appeared to be swollen and loose in the lumen.

The pathologic diagnosis was giant follicular lymphadenopathy associated with Hodgkin's disease.

The postoperative course was uneventful. A course of roentgen ray therapy was given, and since then the patient has felt well and has carried on a normal life.

COMMENT

In the consideration of cases to be included in the group of instances of acute hemolytic anemia of the acquired type Dameshek and Schwartz [1] set down a number of criteria, to which our case seems to respond: (*a*) a history of acute onset, (*b*) signs and symptoms of rapidly progressing severe anemia accompanied by jaundice of the acholuric type, bilirubinemia and increased output of urobilin in the stools and the urine, (*c*) splenomegaly and (*d*) absence of a history of similar diseases occurring in other members of the family.

These being the main features of the case under consideration, the lesions of the spleen and the unusual observation that these were associated with patterns of Hodgkin's disease and of giant follicular lymphadenopathy deserve comment. Extreme congestion of pulp, with thrombosis of veins and capillaries and multiple infarcts; hyperplasia of reticulum cells and erythrophagocytosis; ectopic myeloid metaplasia and occasionally fibrotic nodules, all lesions most frequently mentioned in the literature, were present in our case, congestion of the pulp and hyalinosis of lymph follicles being the predominant patterns. In the absence of any explanation, we call attention to the striking infiltration of granulocytic eosinophils, which were present either sparsely, or in large

groups, most numerously beneath the capsule and around the trabeculae. This feature has not been described in previous reports.

Five years before the development of the hemolytic condition, the patient had been hospitalized for a growth in the neck, diagnosed as Hodgkin's disease. Hematologic investigation at that time failed to reveal any deviation from the normal, and in the following five years the patient was well and carried on a normal life.

A number of authors[5] have commented on the possibility that Hodgkin's disease and related conditions and "hemolytic anemia," which is generally referred to as "symptomatic" are interrelated. Several interpretations have been offered[5]: that the anemia is part and parcel of the cachexia accompanying the lymphogranulomatosis; or that the granuloma itself acts as an irritant to the bone marrow, causing hyperplasia, which results in the production of cells of a less stable character, which in turn are destroyed at an early stage in the spleen and the liver; or that the large spleen, packed with masses of endothelial cells, which might possibly have exceptionally active blood-destroying properties, plays a part in the production of the anemia.

None of these explanations applies in our case. At the time the hemolytic anemia developed, the patient was in good health and the Hodgkin's disease from which he had suffered five years before was apparently healed, or at least well controlled; there was no evidence that the bone marrow was infiltrated by granulomatous tissue, and the spleen was free from granuloma. Therefore, it would seem improper in our case to say that it was Hodgkin's disease which brought about the hemolytic state.

No definite cause and effect relation can be found between the condition of the blood and the growth recurring in the neck two years after the hemolytic crisis. There were still patterns of Hodgkin's disease in the mass removed at this time, but the most striking feature was a numerical and dimensional increase of the lymph follicles, resulting in giant follicular lymphadenopathy.

The association of equally characteristic changes of giant follicular lymphadenopathy and Hodgkin's disease in the same lymph node is certainly uncommon. To check this impression, the sections of lymph nodes removed at necropsy in 5 cases of Hodgkin's disease and of 12 different lymph nodes removed at biopsy, the condition of which was diagnosed as Hodgkin's disease, were reviewed, and in not a single instance were the patterns suggestive of follicular giantism. Yet, mention of the association of the two conditions is made by Symmers,[6] who

5. Dameshek and Schwartz.[1] Watson.[2] Davidson.[3]

6. Symmers, D.: Arch. Path. 26:603, 1938.

expressed the belief that the pattern of Hodgkin's diease was brought about indirectly by the deposition in the modified lymph nodes of megakaryocytes from the marrow and not by alterations of either the fixed or the mobile cells of the lymph nodes of other organs involved.

Another explanation might be offered in our case, namely, that the follicular giantism of the cervical lymph nodes represented a compensatory overgrowth of lymphoid tissue following removal of the spleen. The hyperplasia of reticulum cells of the cervical nodes, accompanied by erythrophagocytosis and by the presence of a considerable amount of blood pigment, might be interpreted as indirect evidence in support of this conception.

While no definite relationship can be seen between the three successive pathologic events in our patient—a granuloma showing the pattern of Hodgkin's disease in 1935, acute hemolytic anemia in 1940 and recurrence of granuloma in 1942, at this time accompanied by giant follicular lymphadenopathy—the three events might be conceived as independent disorders of the reticuloendothelial system, giving rise to manifestations inherent in the developmental and functional potentialities of the system.

It is well established that the widespread elements of the reticuloendothelial system are intimately related to hemoglobin and the metabolism of iron, and because the spleen contains the largest single compact collection of reticulum cells, it is generally assumed that much of the destruction of red cells takes place there, although the bone marrow, the lymph nodes and the liver play important roles in this process.

There is still disagreement as to the causative agent and the nature of Hodgkin's disease, but its relation to the reticuloendotheliosis is generally accepted.

Greppi and Bettoni,[7] discussing an unusual case of Kaposi's disease with extensive visceral manifestations and concomitant hemolytic splenomegaly, reached the conclusion that a generalized disorder of the reticuloendothelial system had manifested itself in the spleen with an exaggeration of the hemoclastic function proper to this organ, while elsewhere it had given rise to the neoplastic growth characteristic of Kaposi's disease.

A similar explanation is proposed for this case. General proliferation of the reticuloendothelial system is known to occur in a variety of clinical entities well classified by Sacks [8] in 1938 under the generic term of "reticuloendotheliosis." It included the so-called lipoidoses and a number of hyperplastic and dysplastic processes of the histiocytes, not associated with any demonstrable metabolic disturbance and apparently

7. Greppi, E., and Bettoni, I.: Arch. Ist biochim. ital. **4**:403, 1932.
8. Sacks, S. M.: Arch. Path. **26**:676, 1938.

occupying an intermediate position between proliferative granuloma and cancerous neoplasia. This classification and similar ones proposed by others were always based on distinctive clinical, pathologic and histochemical patterns pointing to a disorder of the reticuloendothelial system in one or another direction; however, cases are now and then reported which, like ours, are characterized by a number of clinical and pathologic manifestations, independent and unrelated to one another yet all fitting into the conception of a constitutional disarrangement of the reticuloendothelial system manifesting itself in various fashions.

SUMMARY

The case is reported of a 34 year old white man who showed in succession various manifestations of reticuloendothelial disease: first, a cervical granuloma which disclosed the characteristic pattern of Hodgkin's disease; then acute hemolytic anemia, which successfully responded to splenectomy, and last a recurrence of the cervical granuloma in association with giant follicular lymphadenopathy.

SPREAD OF CARCINOMA TO THE SPLEEN

Its Relation to Generalized Carcinomatous Spread

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IN NEOPLASTIC disease other than that of the central nervous system metastasis is a decisive, though not essential, criterion of cancer. The extent of metastasis may be regarded as an indication of the degree of malignancy, and may be manifested by the number of organs in which secondary growths occur. Such an appraisal of the degree of malignancy depends on a survey of the viscera and should be objective.

The examination, however, is frequently conducted with an expectation that certain organs will be elective and others exceptional sites of metastases. This propensity of anticipation has perhaps engendered laxity in the inspection of organs in which secondary growths are not expected, so that the immunity of these viscera may have been spuriously accentuated; such organs—for example, the spleen and the pancreas—may in reality lack a peculiar resistance to the growth of metastases.

The statistical analysis of cases with regard to tumors that spread to the spleen, which is regarded as unfavorable to the development of secondary tumors, has been customarily handled so as to favor such a conclusion. Some workers [1] have studied all cancers encountered over a period of years in the autopsies of an institution and have computed from such inclusive figures the incidence of metastatic involvement of the spleen. Others [2] less discriminately have measured the occurrence of splenic metatasis as a percentage of all the autopsies performed. On

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1. (*a*) Taylor, F.: Lancet **1**:1477, 1904. (*b*) Orlandi, N.: Tumori **13**:545, 1927. (*c*) di Biasi, W.: Virchows Arch. f. path. Anat. **265**:884, 1926. (*d*) Warren, S., and Davis, A. H.: Am. J. Cancer **21**:517, 1934. (*e*) Herbut, P. A., and Gabriel, F. R.: Arch. Path. **33**:917, 1942.

2. (*a*) Buday, K.: Ztschr. f. Krebsforsch. **6**:1, 1910. (*b*) Yokohata, T.: ibid. **25**:32, 1927. (*c*) Sappington, S. W.: J. A. M. A. **78**:952, 1922. (*d*) Krumbhaar, E. B.: Am. Clin. Med. **5**:833, 1927.

the other hand, the proportion of splenic metastases of a particular variety of cancer, such as that of the breast or that of the uterus,[3] has been estimated. It has also become the practice to report single cases of splenic metastasis.[4] While these sundry analyses serve to indicate the general likelihood of encountering splenic metastases in the population at large, in people with tumors and in patients with specific neoplasms, they are of limited statistical significance in the evaluation of the character of the resistance opposed by the spleen to secondary invasion. They lack value in the assessment of splenic metastases particularly because there is no uniformity of the material employed, except for the fortuitous circumstances of being all autopsies, all tumors or all tumors of a particular tissue.

Such categories manifest no similar, comparable predispositions of spread toward the spleen or other organ by which the resistance of the organ may be judged. If the variable to be studied is the degree to which viscera resist metastatic involvement, it is prerequisite that each organ be amply exposed to metastasis, and that, therefore, neither all tumors nor those of a particular histologic type should be considered indiscriminately in the comparison. This issue is to be decided by a consideration of neoplasms which have had equal opportunity to metastasize to all tissues. The various tissues are thereby simultaneously permitted to display their individuality in reacting to the spread of new growths. In this manner each case is a replicative test of the local reaction and is of enhanced statistical value; each case is a natural experiment.

TYPE OF CASES CHOSEN FOR STUDY

The objective of determining the degree to which the spleen reacts against metastases imposes restrictions on and severely limits the choice of material available for study. To assure availability of metastases in a high proportion of instances, it was decided to study only those cases of carcinoma in which there were secondary growths in one or more viscera within both the thoracic and the abdominal cavity, regardless of the primary source. This criterion, that the neoplasm should have spread into the organs of the different body cavities, eliminated the cases without metastases and those with regional spread only, as well as all

3. Azevedo, A. P., and Sales, J. F.: Mem. Inst. Oswaldo Cruz **39**:389, 1943. Gussenbauer, C., and von Winiwarter, A.: Arch. f. klin. Chir. **19**:347, 1876. Paget, S.: Lancet **1**:571, 1889. Handley, W. S.: Cancer of the Breast and Its Treatment, ed. 2, New York, Paul B. Hoeber, 1922. Warren, S., and Witham, E. M.: Surg., Gynec. & Obst. **57**:81, 1933. Saphir, O., and Parker, M. L.: Arch. Surg. **42**:1003, 1941.

4. (*a*) Geipel, P.: Virchows Arch. f. path. Anat. **210**:358, 1912. (*b*) Chaletow, S.: ibid. **217**:140, 1914. (*c*) Kettle, E. K.: J. Path. & Bact. **17**:40, 1912-1913. (*d*) Guttman, P. H.: California & West. Med. **52**:156, 1940.

examples of direct extension. Furthermore, it indicated a strong tendency toward generalized invasion, with equalization of opportunity for metastasis. Of 116 cases of carcinoma collected from a total of 608 autopsies performed in the years 1945 to 1947, 30 met these requirements.

All cases were submitted to routine autopsy. Additional attention was directed to the spleen, however, which was extensively and minutely studied in the gross for macroscopic nodules; at least three and usually five blocks of tissue were taken from each spleen, fixed in solution of formaldehyde U. S. P. diluted 1:10, embedded in paraffin, sectioned and stained with hematoxylin and eosin, Mallory's aniline blue for collagen and Gömöri's stain for reticulin. Several sections were prepared from different levels in each block.

The decision as to what constitutes a microscopic metastasis was solved by adhering to the criterion of Warren and Davis,[1d] who stated in 1934 that they regarded all noncontiguous masses of tumor cells as metastases. As they indicated, it is impossible to determine histologically whether tumor emboli will proliferate or regress, so that any distinction made between tumor emboli and metastases is arbitrary. It was often impossible to determine with certainty whether the clumps of tumor cells occurred intravascularly in the sinusoids or extravascularly in the pulp.

In view of its arterial supply, which it has in common with the spleen, and because it is regarded as a rare site of metastases, the pancreas was also examined specifically for secondary new growth. Both organs derive their principal arterial supply from the same branch of the celiac axis, which would permit them an equal chance of receiving hematogenous tumor emboli—a circumstance that might reveal any particular resistance of the spleen in a discrepancy of incidence.

Furthermore, since both pancreas and stomach are proximal to the spleen and since their common venous system partially drains through the splenic vein, it was necessary to consider the possibility of a retrograde venous conveying of tumor emboli to the spleen from these sites. The incidence of this type of metastasis depends on local anatomic peculiarities and on neoplastic invasiveness, and is independent of generalized spread. This contingency was investigated by a survey of the records of autopsies of persons dying of carcinoma of the stomach and the pancreas, covering a period of twenty years.

RESULTS

The cases analyzed comprise a wide range of morphologic types of carcinoma, derived from an extensive variety of tissues (table 1). These features were so dispersed over the small group with generalized spread as to preclude decisions of particular relationship to splenic metastases

(table 1). Grading of the tumors on a histologic basis was not attempted in view of the heterogenicity of morphologic character and source, and because the extensive incidence of metastases was an adequate guarantee of carcinoma. On the other hand, the incidence of carcinoma and that of splenic secondaries are equally divided between the sexes, indicating that the general tendency toward widespread metastases and toward splenic metastases especially might not be affected by sex. For the selected series of 30 cases the total number with splenic metastases is 15, or 50 per cent of those with generalized spread, a strikingly high figure which suggests that, given opportunity, the organ is recep-

TABLE 1.—*Metastasis of Carcinoma as Determined in 30 of 116 Cases Collected from 608 Autopsies*

Source	Cases of Carcinoma	Cases in Which Metastatic Involvement Was Generalized	Cases in Which Metastasis Involved Given Organ			
			Liver	Lung	Pancreas	Spleen
Stomach	19	7	5	4	3	5
Pancreas	10	2	7	4	0	0
Colon	19	4	7	4	0	3
Breast	9	4	6	5	1	3
Lung	8	4	3	2	3	1
Prostate	7	0	0	0	0	0
Bladder	8	1	3	1	0	0
Kidney	7	0	0	1	0	0
Esophagus	9	2	2	3	1	0
Larynx	3	0	0	0	0	0
Cervix uteri	4	0	0	0	0	0
Ovary	2	2	1	2	1	1
Seminoma	2	2	2	2	1	1
Miscellaneous	9	2	2	2	1	1
Total	116	30	38	30	11	15
Percentage		25.7			9.5	12.9

Note.—In cases of generalized spread the unlisted viscera were involved with less frequency. In no instance was splenic metastasis found without generalized spread.

tive to secondary new growths. The incidence for the entire series of cases of carcinoma is 12.9 per cent.

Since equality of availability of secondary new growths was granted, a comparison was drawn between the behavior of the spleen and that of other viscera. It was apparent (table 2) that the greatest numbers of secondary deposits were found in the regional lymph nodes, and that the lungs and the liver were affected to a nearly similar extent. The remainder of the organs contained tumor nodules with varying but considerably less frequency. The tissues may thus be divided into two groups relative to their incidence of tumor deposits; one category, comprising the lymph nodes, the lungs and the liver, had an 80 per cent or higher incidence; the other, aggregating the remaining viscera, had a 50 per cent or less occurrence. Of the latter group, the spleen had the highest proportion, and was closely seconded by the pancreas

(43 per cent) and the bone marrow (36 per cent). It was noteworthy that the metastatic involvement of the pancreas was statistically approximately equal to that of the spleen; the behavior of these organs was not significantly different toward metastasis. An unexpected finding was that 7, or 23 per cent, of the metastases involved the myocardium, insofar as that organ is regarded as a most rare site of secondary carcinoma.

The relatively few metastases found in bone marrow and kidney reflected not the true occurrence but the proportion found in the routine examination of autopsy tissue. Except in 17 cases, the bones were not systematically inspected with the technic of Willis. Whereas the percentage of secondaries encountered in marrow in the entire series was 36, when regard was paid to careful searching the proportion was

TABLE 2.—*Order of Frequency of Metastatic Involvement of Various Organs in 30 Cases of Carcinoma with Generalized Spread*

Organ	Gross Metastases	Microscopic Metastases *	Percentage
Lymph nodes	25	26	86
Lung	15	25	83
Liver	23	24	80
Spleen	9	15	50
Pancreas	5	13	43
Bone	6	11	36
Adrenal gland	5	8	26
Kidney	5	5	16
Heart (myocardium)	3	7	23
Intestine	3	4	13
Bladder	2	3	10

* The figure for the microscopic metastases represents the total or the sum of the gross and the microscopic metastases. A rare metastasis was seen in the stomach, the appendix and the hypophysis.

raised to 65 per cent of the cases so studied. The kidneys were also examined in the traditional manner by gross inspection after hemisection and microscopic study of a single block from either or from each of the two organs. The lower incidence of renal metastases is not, therefore, conclusive. In an assessment of the extent of metastatic involvement of any tissue the search should be both exhaustive and critical before the absence of secondary growths can be conceded.

The necessity of minute scrutiny of an organ, before assuming that it is devoid of metastases, is further emphasized by the discrepancy, in certain organs, between the proportion of grossly and microscopically detectable secondary new growths. In regional lymph nodes and the liver, microscopic examination has rarely revealed metastases not grossly discernible; whereas in lungs, spleen, pancreas, heart and bone nearly half the metastases escaped gross detection (table 2).

The analysis of the carcinomas of the stomach and the pancreas revealed no peculiar propensty of these neoplasms to invade the spleen through the venous drainage system. This accords well with the pattern of spread in the 19 cases of gastric carcinoma and the 10 of pancreatic cancer in our series. In no instance was splenic metastasis found apart from generalized spread in the gastric cases. None is found for the pancreas.

COMMENT

Because of the infrequency with which splenic metastases are encountered in general surveys of either autopsies or cases of neoplasm, the spleen has been regarded as resistant to secondary invasion. Various hypotheses have been proposed to account for this refractiveness. Kettle [4c] advocated the idea that, owing to motility, the organ pumped out the tumor emboli and refused them refuge; with this view Warren and Davis [1d] agreed. Others have suggested that the splenic vessels are anatomically unsuitable for admission of emboli,[2e] despite the fact that the spleen is a frequent site of infarct in diseases associated with emboli, such as subacute bacterial endocarditis. It has also been proposed that the spleen is unfavorable to the growth of metastases for hormonal, cellular and nutritional reasons,[5] although Woglom [6] discovered no direct or convincing evidence for this conception. As to the proposition that the motility of the organ explains the rarity of metastases, it must be pointed out that if this were so, in such organs as the kidney and the pancreas, which are not especially motile, the incidence of secondary growths should be significantly higher, and in the very motile lungs, lower. Yet Warren and Davis [1d] observed an equal occurrence in the kidney and the spleen, while we found a similar proportion in the pancreas and the spleen and a higher proportion in the lungs. The relative unimportance of motility is further indicated by the occurrence of metastasis in the heart, of which we found 7 instances, 6 per cent of the 116 cases of carcinoma. This high incidence is not in agreement with the findings of other observers, who have indicated the rarity of the condition.[7] So far as a resistance due to structural peculiarity, cellular activity and nutritional opportunities is involved, the lack of disproportion between certain viscera also applies, for it is highly improbable that such diversely different organs as the spleen, the pancreas and the kidney share such an identical resistance. It is evident that the explanation lies elsewhere.

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5. Willis, R. A.: Spread of Tumors in the Human Body, London, J. & A. Churchill, 1934.

6. Woglom, W. H.: Cancer Rev. **4**:129, 1929.

7. Yater, W. M.: Arch. Int. Med. **48**:627, 1931. Burke, E. M.: Am. J. Cancer **16**:205, 1934. Ritchie, G.: Am. J. Path. **17**:483, 1941.

A clue is offered by the observation of di Biasi [1c] that when splenic metastases occur, there are almost always widespread blood-borne secondary tumors in other organs. This was substantiated by Warren and Davis, who found that in every case in which the spleen was involved, there were also metastases in three or more organs. Foulds [8] showed, in an experimental study of the metastatic spread of the Brown-Pearce rabbit tumor, that in no rabbit was tumor found in the spleen in the absence of considerable growth in other and more usual sites. The present study corroborates these observations of the invariable coexistence of widespread hematogenous metastasis in association with splenic metastases, and consequently affirms the view that secondaries usually reach the spleen by embolism through the systemic circulation. The opinion of von Parsch [9] that neoplasms may metastasize to the spleen by spreading in retrograde manner from the liver and adjacent organs through the splenic vein is disputed by Willis [5] and is not substantiated by our studies, nor by the analysis of D'Aunoy, Ogden and Halpert,[10] who studied 40 cases of carcinoma of the pancreas. Among their cases there were 2 with splenic metastasis in which metastatic involvement was also generalized. The sharp limitation of access of tumor emboli conveyed through the arteries only (afferent lymphatic vessels are lacking in the human being, except those to the hilus [11]) is a factor which may elucidate partly the infrequency of metastatic involvement of the spleen.

So far as spread to the spleen by the lymphatic channels is precluded, that by the veins possible but rare and that by the systemic circulation is usual, the mechanism of spread may account for the general infrequency of splenic metastases without ascribing to the organ any peculiarities of resistance. Both the growth and the spread of carcinoma are beset with restrictions. As Takahashi [12] indicated, there are two phases in the process of metastasis. The initial phase is that during which the tumor cells of the primary growth penetrate the vascular endothelium from the outside; the subsequent transportation and arrest of emboli are mechanical. "The second phase, and it is critical for the formation of secondary growths, is that in which tumor cells establish organic union with the vessel wall after their arrest, penetrating the endothelium from the inside." Willis agreed that the second phase is the most precarious period, when during the postembolic intravascular sojourn the metastatic new growth is adapting to the new environ-

8. Foulds, L.: Tenth Scientific Report on the Investigation of the Imperial Cancer Research Fund, 1932, p. 21.

9. von Parsch: Centralbl. f. allg. Path. u. path. Anat. **24**:965, 1913.

10. D'Aunoy, R.; Ogden, M. A., and Halpert, B.: Am. J. Path. **15**:217, 1939.

11. Rouviere, H.: Anatomy of the Human Lymphatic System, translated by M. J. Tobias, Ann Arbor, Mich., Edwards Brothers, Inc., 1938, p. 206.

12. Takahashi, M.: J. Path. & Bact. **20**:1, 1915-1916.

ment. If this conception is true, the spread of tumors is opposed by a series of obstacles or barriers. The reality of these barriers is attested to by Schmidt's [13] critical study of pulmonary metastases in a series of cases of intra-abdominal carcinoma, in which he found that, of the great number of tumor emboli which reached the lung, only a portion developed as successful new growths. Before a neoplasm can reach the systemic circulation, it must pass a series of such barriers in various organs—for example, the lymph nodes, the liver and the lungs—the number and the sites depending on the source of the neoplasm. In some instances, metastases may localize two or even three times, called primary, secondary and tertiary metastases by von Recklinghausen [14] and by Zahn,[15] before any reach the lungs or a position from which invasion of the systemic circulation is possible.

It is apparent, therefore, that the division of metastatic sites into groups of high and low incidence is part of this general pattern of tumor spread. The lymph nodes, the lungs and the liver are subjected to the early primary and secondary metastases and have a high rate, whereas other viscera are encountered by tumor emboli late, after these have saturated the barriers and entered the systemic circulation, because of which the rate is relatively low. But, when comparison is made between neoplasms that have permeated the barriers and spread into the systemic circulation, with all tissues then equally exposed to metastatic involvement, the discrepancy between the rates of incidence of neoplasms of the various organs is diminished. In such cases the spleen and the pancreas are not less susceptible to metastases than other viscera the involvement of which depends on arterial transmission of tumor emboli.

SUMMARY AND CONCLUSIONS

In 30 cases of carcinoma in which metastases occurred in one or more organs in more than one body cavity, the incidence of splenic and pancreatic metastases was 50 and 43 per cent, respectively.

The low occurrence of splenic metastases as compared with those observed in lymph nodes, liver and lungs was due to inequality of exposure to metastases. When exposure was equalized, the spleen was not less susceptible than other viscera.

13. Schmidt, M. B.: Die Verbreitungswege der Karzinome und der Beziehung generalisierte Sarkome zu den leukämischen Neubildungen, Jena, Gustav Fischer, 1903.

14. von Recklinghausen, F.: Virchows Arch. f. path. Anat. **100**:503, 1885.

15. Zahn, F. W.: Virchows Arch. f. path. Anat. **115**:71, 1889.

LAENNEC CIRRHOSIS

Its Histogenesis, with Special Reference to the Role of Angiogenesis

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MY OBJECT was to study the histogenesis of Laennec cirrhosis from the biologic as opposed to the static and purely descriptive anatomic point of view. For this purpose I employed two methods: (1) the examination of lesions from the earliest to the most mature phase and (2) the use of serial sections. These measures served to orient the livers in point of space and time and enabled me not only to study the fate of the intrinsic vascular components of the diseased organs but also to trace the development of new vessels from the formation of new capillaries to vessels of the mature type. By these methods one is enabled to submit an interpretation of the lesions of Laennec cirrhosis that has not hitherto been presented, particularly in respect to the predominant process of Laennec cirrhosis, namely, the formation and distribution of the connective tissue. Moreover, these measures have helped to throw light on the genesis of bile canaliculi and of new intrahepatic anastomotic channels that develop not only within the lobules but also between the portal circulation and the hepatic veins. I have studied 75 livers in all stages of Laennec cirrhosis; 8 of these, presenting various maturities of the process, were studied by serial section. The sections were stained by the hematoxylin-eosin, Van Gieson and Mallory-azocarmine methods and with stains for elastic tissue.

STAGE 1. FATTY LIVER

It is generally agreed that a fatty condition of the liver is the usual precursor of Laennec cirrhosis.[1] One owes a debt to Connor [1a] for throwing light on the hitherto obscure relation between chronic alcoholism and the development of Laennec cirrhosis. He showed that it was not the alcohol but the notoriously deficient diet of persons who suffer from alcoholism [2] that is responsible and that persons who consume an

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1. (*a*) Connor, C. L.: J. A. M. A. **112**:387, 1939. (*b*) Rössle, R.: Die Entzündungen der Leber, in Henke, F., and Lubarsch, O.: Handbuch der speziellen Pathologie und Histologie, Berlin, Julius Springer, 1930, vol. 5, pt. 1. (*c*) MacCallum, W. B.: Text Book of Pathology, ed. 7, Philadelphia, W. B. Saunders Company, 1940.

2. Romano, J.: Am. J. M. Sc. **194**:645, 1937.

adequate and balanced diet can even take an abundance of alcoholic beverages without causing cirrhosis. Fatty liver, however, is not the exclusive attribute of persons addicted to the consumption of alcoholic liquors, since it is very common in people who are undernourished from whatever cause—for instance, in those who show ulcerative colitis, cachectic states, diabetes mellitus, hypothyroidism, lesions of the pituitary gland, chronic sepsis and chronic tuberculosis. Cirrhosis is known to occur in such conditions. The most convincing demonstration that fatty liver is the earliest stage of Laennec cirrhosis due to nutritional disorders is that reported by Gillman and Gillman,[3] who performed biopsy of the liver at intervals over periods of years on patients with pellagra in South Africa. Although their main purpose was to show that eventually the hepatic lesions were indistinguishable from hemochromatosis, biopsy revealed that the earliest stage was fatty liver, which slowly progressed to classic Laennec cirrhosis.[4] Their investigation, in passing, eloquently reveals the value of the biologic study of disease. The causal relation of nutritional disorders to Laennec cirrhosis probably explains the frequency of Laennec cirrhosis in natives of tropical countries.[5]

Connor's observations have stimulated the study of experimental Laennec cirrhosis as produced with various types of dietary deficiency.[6] In all such deficiencies fatty liver is produced, sometimes with central necrosis,[6a] and the ensuing cirrhosis resembles Laennec cirrhosis in every particular except the ceroid deposits.

As far as these experimental methods permit one to say, apparently any method whereby prolonged and pronounced fatty liver is produced may in time stimulate the production of periportal cirrhosis of the liver.

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3. Gillman, J., and Gillman, T.: Arch. Path **40**:239, 1945.

4. The reports of the rare cases in which cirrhosis was observed in children are unsatisfactory for appraisal because little attempt had been made to differentiate between the fibrosis following toxic hepatitis and portal cirrhosis. As far as one can gather, most of the reported cases represented the terminal stage of toxic hepatitis.

5. (*a*) Castellani, A., and Chambers, A. J.: Manual of Tropical Medicine, Baltimore, Williams & Wilkins Company, 1919. (*b*) Manson, P.: Tropical Diseases, ed. 11, ibid., 1940. (*c*) Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, Philadelphia, The Blakiston Company, 1942.

6. (*a*) György, P., and Goldblatt, H.: J. Exper. Med. **75**:355, 1942. (*b*) Rich, A. R., and Hamilton, J. D.: Bull. Johns Hopkins Hosp. **66**:185, 1940. (*c*) Lillie, R. D.; Daft, F. S., and Sebrell, W. H.: Pub. Health Rep. **56**:1255, 1941. (*d*) Earle, D. P., Jr., and Victor, J.: J. Exper. Med. **73**:161, 1941. (*e*) Holliday, N.: J. Nutrition **16**:285, 1938. (*f*) Gavin, G., and McHenry, E. W.: J. Biol. Chem. **132**:41, 1940. (*g*) Webster, G. T.: J. Clin. Investigation **21**:385, 1942. (*h*) Fouts, P. J.: J. Nutrition **25**:217, 1943. (*i*) Spellberg, M. A.; Keaton, R. W., and Ginsberg, R.: Arch. Path. **33**:204, 1942. (*j*) Best, C. H., and Ridout, J. H.: Ann. Rev. Biochem. **8**:349, 1939. (*k*) Griffith, W. H., and Wade, N. J.: J. Biol. Chem. **131**:567, 1939.

The stimuli are still unknown, but from the observations thus far reported, the probability is strong that the production of experimental cirrhosis depends on a sufficiently prolonged interaction of a vitamin deficiency and a deficiency of a lipotropic factor. The time factor was demonstrated by Chaikoff, Connor and Biskind,[7a] who maintained pancreatomized dogs with insulin over long periods. The earliest evidences of cirrhosis arose only after an interval of one and a half years. Obviously, it is problematic whether in the human being a fatty liver of whatever origin will eventually become cirrhotic, given sufficient time. Undoubtedly the quantitative factor—an amount of fat sufficient to distort the parenchyma to the necessary degree—is a conditioning element, aside from the continuance of the factor or factors that produced the fatty change. Human cirrhosis parallels experimental cirrhosis in its favorable response to a nutritious diet and a vitamin B concentrate.[8] That nutritional disturbances are causally related to hepatic fibrosis is further shown in the effect of some vitamins and amino acids in protecting the liver against the destructive effect of toxic substances. Thus, Von Glahn and Finn [9] lowered the incidence of cirrhosis produced by lead arsenate by adding brewers' yeast to the diet. Miller, Ross and Whipple [10] gave animals almost complete protection against hepatic injury induced by chloroform by administering methionine and/or, with less effect, cystine.

The livers of patients who die with Laennec cirrhosis vary largely in their fat content. Indeed, death may occur with a fatty liver without cirrhosis.[1a] The amount of fat depends on the stage in which death occurs. When death comes early, the cause is ascribable mostly to a "beriberi heart" rather than to hepatic insufficiency. In the late stage the depletion of the fat is probably more dependent on the institution of a well balanced diet than on any other factor.[1a] This was effectively demonstrated by Gillman and Gillman [3] in cases of pellagra. Whether depletion of the fat reserves plays a role in human Laennec cirrhosis one is not in a position to say.[11] Evidently depletion of fat alone does not always prevent continuance of the cirrhotic process, since histologic evidences of activity are often seen in livers the fat content of which has been reduced to a minimum. The arrest of the cirrhotic process probably depends not only on the stage in which alcoholic abstinence and an adequate diet have been instituted but also on unknown factors

7. (*a*) Chaikoff, I. L.; Connor, C. L., and Biskind, G. R.: Am. J. Path. **14**:101, 1938. (*b*) Chaikoff, I. L.; Eichorn, K. B.; Connor, C. L., and Entenman, C.: ibid. **19**:9, 1943.

8. Patek, A. J., Jr., and Post, J.: J. Clin. Investigation. **20**:481, 1941.

9. Von Glahn, W. C., and Finn, F. B.: Am. J. Path. **15**:771, 1939.

10. Miller, L. C.; Ross, J. F., and Whipple, G. H.: Am. J. M. Sc. **200**:739, 1940.

11. Dibble, J. H.: J. Path. & Bact. **35**:451, 1932. Dibble, J. H., and Libman, J.: ibid. **38**:269, 1934.

that stimulate the regenerative powers of the undamaged portions of the liver.[12] Under favorable circumstances the cirrhotic process may be arrested, and if the damage has not been too extensive, a compensated phase may be established, which clinically is termed "latent cirrhosis."[13]

The histologic features of the extreme grade of fatty liver are familiar. The fat deposited within the cell is usually sufficient to push the nucleus to one side. In later stages, hyaline deposits arise within the cell. These were regarded by Mallory[14] as characteristic of alcoholic cirrhosis, but they occur in other conditions. The swelling of the hepatic cords may be so great as to compress the sinusoids completely, so that the entire lobule appears almost avascular. The intracapsular tension is increased; this is reflected in the tense capsule, the everted cut edges and the parenchyma protruding beyond the cut surface. The significance of this will be discussed later.

STAGE 2. INFLAMMATORY ROUND CELL INFILTRATION OF THE PERIPORTAL SPACES

The beginning of cirrhosis in a fatty liver is represented by round cell infiltrations of the periportal spaces. Since most of the infiltrating cells are of the lymphoid type, with a lesser number of plasma and a few polymorphonuclear cells, such infiltrations may be regarded as inflammatory in type. Round cell infiltration of the portal spaces is so common that many deem a moderate degree of it as within the range of normal and therefore of slight significance. It is especially common in young children. That periportal round cell infiltrations cannot be regarded as normal is manifest in their complete absence in the majority of livers of adults. Such infiltrations are common in all varieties of infections[15]; they occur in biliary cirrhosis, in infectious hepatitis and in passive venous congestion of the liver. They bear no relation to general hyperplasia of the lymphatic tissues except in leukemia. In leukemia the infiltrations can be distinguished from those of fatty liver by the observation that there is no admixture of plasma or polymorphonuclear cells and that the infiltrative cells stain positively by the oxidase reaction. The significance and the ultimate fate of many of the inflammatory types of round cell infiltrating the portal spaces remain to be

12. Whether Laennec cirrhosis can arise in a nonfatty liver is questionable. One often sees comparatively intact livers with early cirrhotic changes, but one cannot be assured that these livers had not previously been fatty. Livers with normal parenchymal cells often show an inflammatory cell reaction in the portal spaces, but, obviously, whether such a reaction may be called cirrhosis is doubtful, since one cannot follow the evolution of the process.

13. Ratnoff, O. D., and Patek, A. J., Jr.: Medicine **21**:207, 1942.

14. Mallory, F. B.: Bull. Johns Hopkins Hosp. **22**:69, 1911.

15. Kettler, L.: Virchows Arch. f. path. Anat. **291**:706, 1933.

clarified. At present one is interested only in their significance in the fatty livers.

Of one thing the observer may be reasonably sure, namely, that, given sufficient time, all fatty livers will show this inflammatory reaction within the portal spaces. The significance of such infiltrations has been minimized, in all probability, because it was overshadowed by the greater interest in the fibrosis. But round cell infiltration has been reported by all observers who have investigated experimentally the process by which a fatty liver is transformed into Laennec cirrhosis by deficient diets; if some do not mention it, their illustrations reveal it unmistakably. As to human Laennec cirrhosis, Gillman and Gillman [3] observed such infiltrations in the earliest stages of pellagra, and Hall and Ophüls,[16] in early stages of alcoholic fatty cirrhosis. Fatty cirrhosis accompanied by round cell infiltration was observed by Chaikoff, Entenman, Rinehart and Reichert [17] and by Graef, Negrin and Page [18] after experimental injury of the hypophysis. The latter, however, stated that the disturbance of the food habits of the animals could not be excluded as a factor in the production of the lesions. That a high fat diet alone may produce fatty cirrhosis with round cell infiltration was demonstrated in dogs by Chaikoff, Eichorn, Entenman and Connor.[7b] It is apparent that while fatty liver is invariably associated with inflammatory round cell infiltration of the portal spaces, given sufficient time, the precise physicochemical stimulus that creates this association is speculative. It is certainly not an infective agent, since evidence of such an agent has never been found, and the manner in which round cell infiltrations have been produced experimentally in fatty livers precludes such an agent. It is not necrosis, since the infiltration is usually unaccompanied by any evidence of necrosis, and when focal necrosis does occur in the fatty liver the round cell infiltration does not take place within or immediately around the area. György and Goldblatt [6a] commented on the fact that although in their experiments the necrosis was in the center of the lobule, the round cell infiltrations were in the portal spaces. In a single microscopic section these areas are noted in the whole or more usually in a division of the portal spaces, but in serial sections of fatty livers, especially those with beginning cirrhosis, these infiltrations are invariably noted in the periphery of the space adjacent to the liver cords and especially in the angles of the portal spaces, where the interlobular or septal branches of the hepatic artery, the bile duct and the portal vein arise (fig. 1). In other words, these infiltrations, strictly speaking, are not only limited to the portal spaces but extend into the adjacent liver

16. Hall, E. M., and Ophüls, W.: Am. J. Path. **1**:477, 1929.

17. Chaikoff, I. L.; Entenman, C.; Rinehart, J. F., and Reichert, F. L.: Proc. Soc. Exper. Biol. & Med. **54**:170, 1943.

18. Graef, I.; Negrin, J., and Page, I. H.: Am. J. Path. **20**:823, 1944.

lobules. In addition, the infiltrations are exceedingly common between the walls of the hepatic or the sublobular veins and the liver cords (fig. 2). The predilection of these sites suggests that the infiltrating cells may in part be derived from the sinusoids or from the septal vascular branches.

In how far these cells are derived by emigration or by reversion of the capillary endothelium or by proliferation of the fixed mesenchymal cells one is not in a position to say. The present discussion concerns their factual presence and their potentiality.

STAGE 3. CAPILLARIZATION

If one views these inflammatory infiltrations in a somewhat later phase and with the high power of the microscope, one can note a fibroblastic transformation. The cells are scattered more loosely, and a loose fibrillar network is noted between and connecting the individual cells (figs. 3 and 4). In a later phase the cells have undergone a more advanced fibroblastic stage, and then either a portion or the entire area contains a network of newly formed, thin-walled capillaries. That these do not represent transformed sinusoids is shown not only by the fibroblastic structure of the walls but also by the fact that their lumens course, not concentrically, but in every conceivable direction (figs. 5 and 6). This capillary network at first lies precisely at the site of the previous inflammatory cellular reaction, namely, between the portal space and the hepatic cords or between the branches of the hepatic artery and the hepatic cords. These areas are now richly interspersed with fibroblasts, and the morphologic aspect is that of young granulation tissue.

Although the periportal growth of tissue observed in early Laennec cirrhosis has often been described as granulation tissue, this capillarization, an admittedly indispensable feature of the development of granulation tissue, has been apparently entirely overlooked. Rössle [1b] mentioned it in passing but gave it a subsidiary role in the genesis of the connective tissue content. Pfuhl [19] in his comprehensive histologic study of the normal liver referred to such capillarization, but he expressed the belief that it may be a normal finding. He said: ". . . between the connective tissue of the portal spaces or septa interlobularia and the adjacent liver-celled trabeculae, there may occur cellular infiltrations that penetrate between the trabeculae. These infiltrations contain well filled capillaries, and in their centers one sees dilated portal branches or septal precapillaries." Schmidt [20] observed round cell infiltration with capillarization within such areas in the

19. Pfuhl, W.: Der Leber, in von Möllendorff, W.: Handbuch der mikroskopischen, Anatomie des Menschen, Berlin, Julius Springer, 1930, vol. 6, p. 338.

20. Schmidt, M. B.: Beitr. z. path. Anat. u. z. allg. Path. **11**:199, 1891-1892.

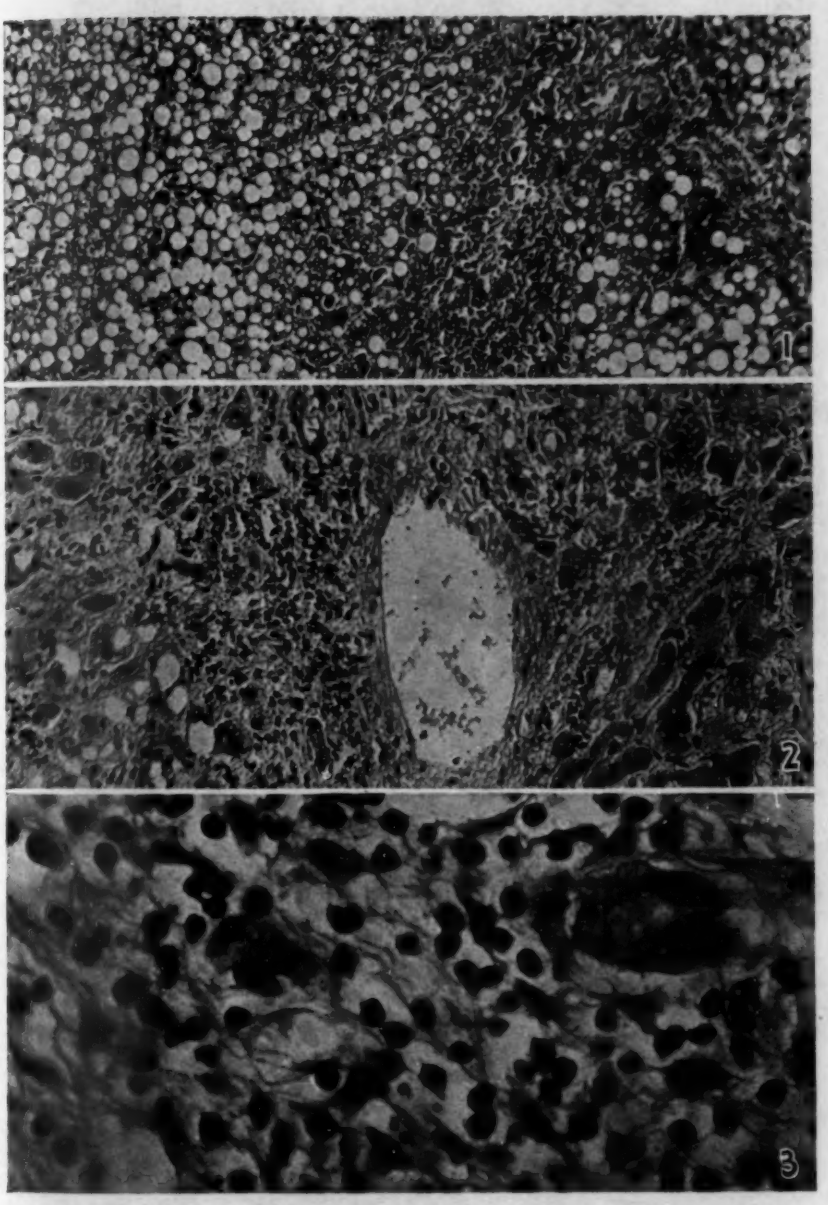
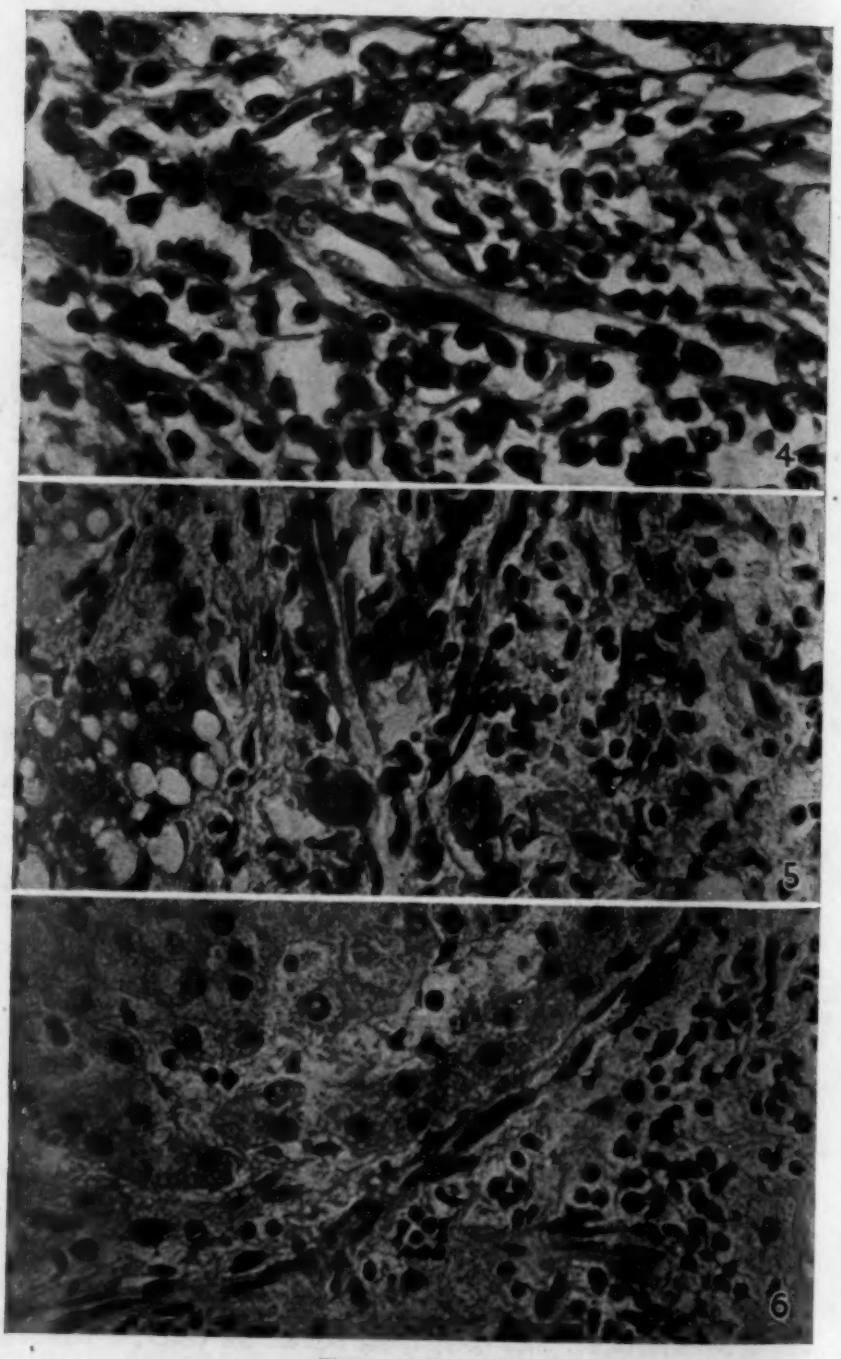


Fig. 1.—Fatty liver showing a portal space with inflammatory round cell infiltration of periportal and interlobular septal areas.

Fig. 2.—Fatty liver showing inflammatory round cell proliferation around a hepatic vein.

Fig. 3.—Beginning fibroblastic transformation of a periportal round cell area, with a delicate reticular network appearing between the cells, and beginning capillarization.



Figures 4, 5 and 6

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embryonal liver. He expressed the belief that the capillaries arise from the endothelium. Dietrich [21] described similar findings in the livers of rats after splenectomy and after injection of trypan blue. Kuczynski [22] observed capillarization with round cell infiltration in various chronic infections or hemolytic states, and he expressed the belief that such changes may be beginnings of a cirrhotic process.

I deem the development and fate of these capillaries to be the most important determining factor in the genesis of the lesions of Laennec cirrhosis, since they help one to interpret not only the fibrosis but its distribution. Furthermore, the farther evolution of these structures not only determines the main vascular content of the fibrosis but also furnishes the clue to a secondary angiogenesis that forms an internal anastomotic network between the portal vein and the hepatic artery.

This necessitates a discussion of angiogenesis. Angiogenesis follows almost similar patterns in granulation tissue and in embryonic development, at least in the early phases of this development. In the embryo it begins in the area pellucida by the formation of blood islands. These are formed by a process of differentiation of the mesenchyma. Eventually the outer layer forms a space which is lined by endothelium and becomes a primitive blood vessel. These differentiated cells may be termed angioblasts (fig. 7). The remaining cells are converted into hemocytoblasts, which are the progenitors of the various blood cells. These primitive endothelium-lined blood vessels arising from numerous blood islands form a capillary plexus which fuses to form the main vascular trunk of the embryo and the adult. Later when the circulation has been established, capillaries grow by endothelial sprouting from previously formed capillaries; the sprouts become hollowed out and unite with similar sprouts coming from neighboring capillaries.[23] Of deeper significance for the present purpose is the demonstration that the primitive vessels do not require vascular endothelium for their origin and development, since it

21. Dietrich, H.: Mitt. a.d. Grenzgeb. d. Med. u. Chir. **40**:183, 1927-1928.

22. Kuczynski, M. H.: Beitr. z. path. Anat. u. z. allg. Path. **65**:315, 1919.

23. (*a*) Benninghoff, A., in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1930. (*b*) Bailey, P., and Miller, A. M.: Text Book of Embryology, ed. 5, Baltimore, William Wood & Company, 1929. (*c*) Clark, W. E. L.: The Tissues of the Body, New York, Oxford University Press, 1939. (*d*) Pettler, B. M.: Human Embryology, Philadelphia, The Blakiston Company, 1946.

Fig. 4.—A stage a little more advanced than that shown in figure 3, showing early capillarization; early Laennec cirrhosis.

Fig. 5.—Well marked capillarization in a periportal space in a fatty liver; early Laennec cirrhosis.

Fig. 6.—Well marked capillarization of a periportal space in a liver that is nonfatty; early Laennec cirrhosis.

has been repeatedly shown that new blood vessels may arise autochthonously in nonvascular embryonal mesenchyma.[24] Apart from the embryo and especially in the formation of granulation tissue, angiogenesis proceeds along similar lines, that is, autochthonously and by sproutings from previously formed capillaries. Billroth,[25] in 1856, was the first to demonstrate these modes of angiogenesis. Since then his findings have been confirmed by numerous observers [26] ; and, moreover, they are independent of the nature of the irritation.[27]

STAGE 4. FURTHER DEVELOPMENT OF THE PROCESS OF CAPILLARIZATION

In the early phases the areas of capillarization are morphologically typical of early, aseptic, loosely formed cellular granulation tissue. In addition to the capillaries, one notes abundant young fibroblasts, plasma cells and monocytes and a sparse sprinkling of polymorphonuclears. Frequently one sees smaller islands of liver cells enclosed within these areas. Some of these strands penetrate in the direction of interlobular spaces and eventually communicate with similar strands advancing from the neighboring portal spaces. A strand may penetrate directly into the lobule or unite with a neighboring strand. Very often in serial sections one can trace strands of granulation tissue connecting the portal space and the smaller branches of hepatic veins (fig. 8). This accounts for the frequent presence of hepatic veins within the strands of fibrous tissue in advanced cirrhosis. That there is a circulatory communication between the latter strands is shown by figure 9, in which the new capillaries are noted emptying into the hepatic vein, and also by fairly large venules (fig. 10) that communicate between the portal and the hepatic veins. These communications represent an attempt to create a minor form of Eck fistula. Such strands of connective tissue spring-

24. (*a*) Rückert, J., and Mollier, S., in Hertwig, W. A. O.: Handbuch der vergleicherenden und experimentelle Entwicklungslehre der Wirbeltiere, Jena, Gustav Fischer, 1906, vol. 1, pt. 1, p. 126. (*b*) McWhorter, J. E., and Whipple, A. O.: Anat. Rec. **6**:121, 1912. (*c*) Schulte, H. von W.: Early Stages of Vasculogenesis in Cat (Felis domestica) with Especial Reference to Mesenchymal Origin of Endothelium, American Anatomical Memoir 3, Philadelphia, Wistar Institute of Anatomy and Biology, 1914. (*d*) Hahn, H.: Anat. Anz. **33**:153, 1908. (*e*) Hueck, W.: Beitr. z. path. Anat. u. z. allg. Path. **66**:330, 1920.

25. Billroth, T.: Untersuchungen über die Entstehung der Blutgefässe, Berlin, G. Reimer, 1856.

26. (*a*) Dawson, J. W., cited by Beattie, J. M., and Dickson, W. E.: A Text Book of Special Pathology, ed. 3, St. Louis, C. V. Mosby Company, 1927. (*b*) Borst, M.: Ergebn. d. Path. u. Anat. **4**:461, 1897. (*c*) Marchand, F.: Neubildung der Gefässe, in Deutsche Chirurgie, Stuttgart, F. Enke, 1901, vol. 16, p. 143. (*d*) Clark, E. R.: Ann. Int. Med. **9**:1043, 1936. (*e*) Rückert and Mollier.[24a] (*f*) Clark.[23c]

27. Werthmann, A.: Virchows Arch. f. path. Anat. **270**:605, 1929.

ing from the hepatic veins were recently described by Ashburn and his co-workers [28] as observed in a form of dietary cirrhosis of rats and in carbon tetrachloride cirrhosis of rats and guinea pigs. Rössle [1b] termed such communicating strands between the portal and the hepatic veins "bivenous." I, also, have observed strands of granulation tissue between the portal spaces and the central veins, so that these, also, later become incorporated within the connective tissue.

In serial sections, not every segment of the portal space is affected. A portal space may even show profound capillarization and when traced to another plane be found entirely unaffected. Furthermore, the same liver may show different stages of the process. In one portal space one may find only the inflammatory cellular reaction, in another capillarization with young granulation tissue, in a third a sclerotic transformation (discussed later).

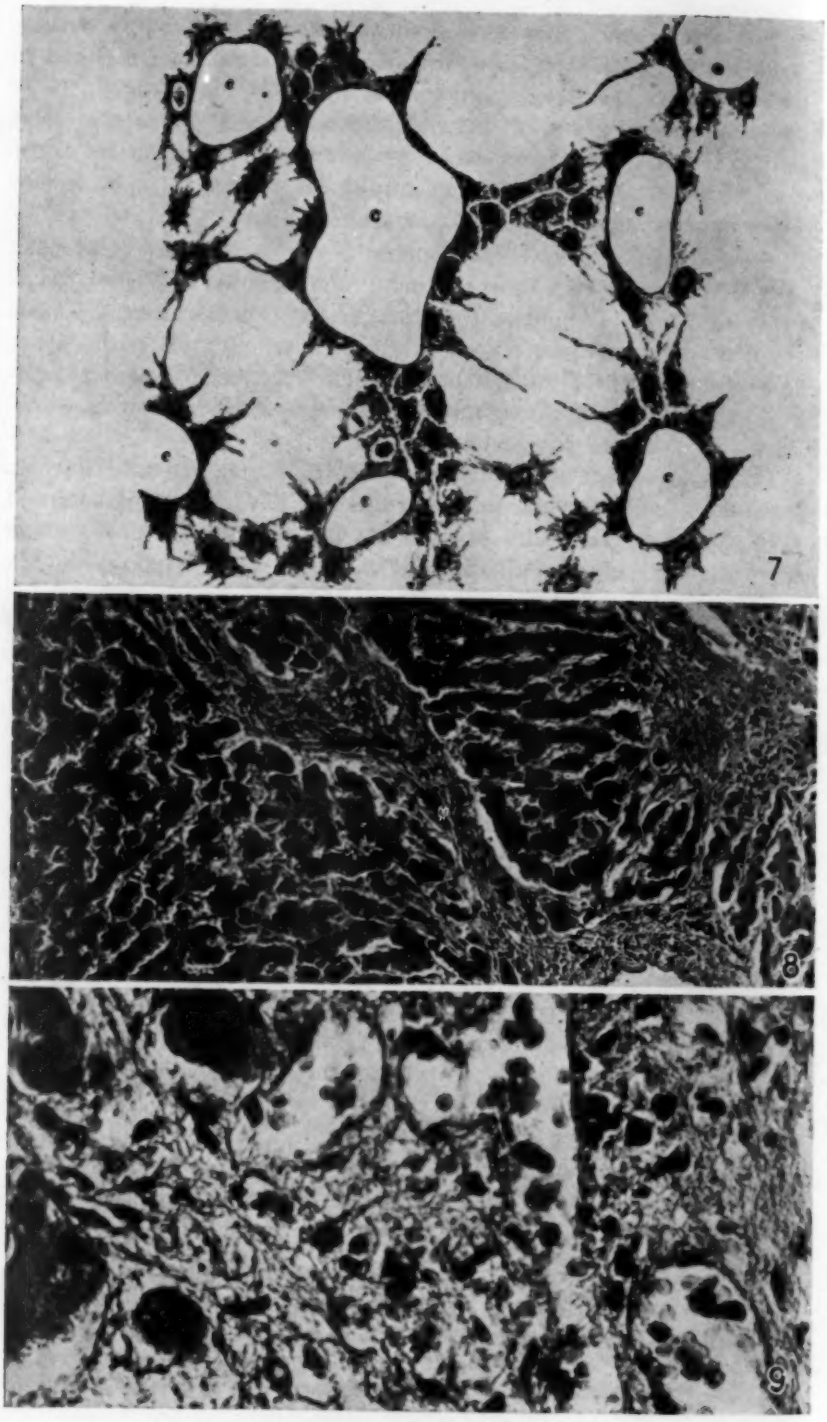
This development and distribution of the granulation tissue furnish the pattern of the conventional mature lesions of Laennec cirrhosis and account for the eccentricity or even absence of the central veins, the peripheral distribution of the fibrosis, the *Umbau* (rebuilding) or distortion of the lobular pattern, the frequent inclusion of the hepatic and the central veins in the connective tissue strands and the absence of sclerotic changes in some of the periportal fields.

The fate of this capillarization is precisely that which has so frequently been observed not only in ordinary granulation tissue but in embryonic angiogenesis. It proceeds subject to the laws formulated by Thoma [29]: 1. The width of a vessel is dependent on the rate of blood flow; when the rate lessens, the width diminishes. 2. The thickness of the wall depends on the blood pressure. 3. The new formation of capillaries depends on the differences of pressure between the interior of the capillary and the surrounding tissue spaces; if in a certain area the pressure of the tissue fluid is higher than the intracapillary pressure, the formation of capillaries does not occur; if, on the other hand, the intracapillary pressure is higher, new capillaries are engendered. These laws have withstood rigid tests and are generally accepted by morphologists. The endothelial cells of the capillaries that disappear do not degenerate but assume irregular branching forms and revert to become cells of the mesenchymal type.[30] It is generally recognized that the portions of the primitive capillary network that persist precede the larger vessels that form. Bailey and Miller [23b] stated that "the vitelline plexus of capillaries antedates any of the larger vitelline vessels."

28. Ashburn, L. L.; Endicott, K. M.; Daft, F. S., and Lillie, R. D.: Am. J. Path. **13**:159, 1947.

29. Thoma, R.: Beitr. z. path. Anat. u. z. allg. Path. **66**:378, 1920. Benninghoff.[23a] Bailey and Miller.[23b] Clark.[23c] Pettler.[23d] Werthmann.[27]

30. Rössle.[1b] Benninghoff.[23a] Bailey and Miller.[23b] Werthmann.[27]



Figures 7, 8 and 9

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According to the first and second laws of Thoma, the vessel walls elongate and thicken, and, by the conversion of the surrounding mesenchymal cells (pericytes), fibrillar connective tissue and elastic and muscular coats are formed, and the vascular bed develops into the mature vascular system.[31] Bailey and Miller [23b] remarked that the "thickened walls of the larger vessels may be regarded as adaptations to the functions they perform."

In the angiogenesis of granulation tissue the process is similar but is modified because the stimulus is not that of growth but that of repair. In the beginning angiogenesis again proceeds according to the laws of Thoma, but, owing to the increase of tissue tension, a larger number of capillaries are obliterated, and the composite cells, instead of reverting to the embryonal mesenchyme, become converted to collagen and eventually to sclerotic fibrous tissue through a series of intermediary cellular stages the components of which have been called by different observers polyblasts,[32] clasmatocytes [33] and plasma cells.[34] The capillaries that survive through the exigencies of either increased blood flow or intracapillary pressure furnish the main blood supply of the strands of newly formed granulation tissue of the liver in Laennec cirrhosis. With further maturation and increasing sclerosis, even these vessels slowly atrophy and the resulting strand becomes almost or completely avascular. The progressive sclerosis is the result of the progressive fibroblastic transformation of the cells involved in the aforementioned processes of angiogenesis until eventually the granulation tissue becomes completely fibrous. In time some or all of the fibrous strands become elastic. I have not observed the development of the muscular coat in these newly formed vessels of the liver.

During the course of this evolution the liver passes from a hypertrophic to an atrophic phase. There is no reason to presume that hypertrophic and atrophic Laennec cirrhosis are different diseases, since

31. Sandison, J. C.: Am. J. Anat. **41**:475, 1928. Benninghoff.[23a] Bailey and Miller.[23b] Clark.[23c] Pettler.[23d]

32. Maximow, A., in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol. 2.

33. Ranvier, L.: Arch. d. anat. micr. **3**:122, 1900.

34. (*a*) Adami, J.: Principles of Pathology, ed. 2, Philadelphia, Lea & Febiger, 1910, vol. 1. (*b*) Dawson.[26a]

Fig. 7.—Autochthonous capillarization: The spaces designated by *c* represent the capillary "anlages" in the cell strands of the mesoblast in the area pellucida of a 28 hour fowl; from Thoma.[29]

Fig. 8.—Laennec cirrhosis. Strands of granulation tissue containing new vessels extend between a portal space and a hepatic vein.

Fig. 9.—High power magnification of a section of the strand shown in figure 8. Note capillaries opening into a hepatic vein.

the transition from one to the other is often clinically manifest. The hypertrophy is largely the consequence of the increased fatty deposit. The subsequent decrease may be ascribed partly to the depletion of the fat and partly to the sclerotic contraction of the newly formed elastic granulation tissue. Although regenerative changes of the liver parenchyma usually occur in the maturer phases of Laennec cirrhosis, the regeneration is microscopic in its dimensions and does not appreciably enlarge the organ.

In this interpretation the connective tissue structure of Laennec cirrhosis is the result of the multipotential properties of the cells of the adult mesenchyme, which maintains in a large measure its embryonal characteristics. The validity of this interpretation depends on whether these potentialities have been demonstrated. Despite the confusing nomenclature that has been imposed on the various derivative cells of the primitive and the adult mesenchyme, it has been amply demonstrated on morphologic evidence, by tissue culture and by the transparent chamber in the living animal that the lymphoid cell, the polyblast, the plasma cell, the clasmatocyte, the monocyte, the fixed tissue cell, the wandering cell, the angioblast and the endothelial cell are not specific structures but represent various phases of development, under the influence of various stimuli, of the primitive mesenchyme; and further that they are capable in a large measure of reassuming the potentialities of the embryonal mesenchyme.[35] One of these potentialities, as I have tried to show, is angiogenesis, and it is only through the intermediacy of angiogenesis that the increased connective tissue content of Laennec cirrhosis is evolved.[36]

By serial sections one can invariably trace the vessels of the fibrous strands into the portal vein. In not a single instance have I found that these strands are supplied with arterial blood. The interlobular branches of the hepatic artery are difficult to find in Laennec cirrhosis, but when they are present they appear intact.

It seems curious that there are practically no studies concerning the nature and the source of the finer vascular content of the connective tissue strands in Laennec cirrhosis in comparison with the number of investigations of the changes of the grosser integral vasculature of the organ. Apparently most observers assume that new blood vessels follow

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35. Foot, N. C.: J. Exper. Med. **34**:625, 1921. Benninghoff.[23a] Hueck.[24e] Marchand.[26c] Werthmann.[27] Maximow.[32] Adami.[34a]

36. In transforming from the granulation to the sclerotic stage the connective tissue forms splits, which become partially or completely filled with cells containing deeply staining nuclei and resembling small lymphoid cells. These cells line the slits like endothelium. These structures resemble the "Saft Spalten" (Sap Clefts) and were once regarded as primitive lymphatic channels. The evidence at present is against this interpretation.[23a] I have not noted any with a fluid content.

the paths laid down by the connective tissue, without any consideration of the origin of these vessels.

This interpretation of the genesis of connective tissue in Laennec cirrhosis differs from those held in the past. Kretz [37] in 1905 and MacCallum,[16] in 1940 regarded the connective tissue as a process of repair and as the result of "regeneration of successive focal destructive lesions around the central vein leading to a disappearance of the surrounding cell mantle. The framework persists but soon collapses, and there is produced an irregular lobular mass in which the central vein is in places more thinly covered by the radial strands of liver cells or even completely exposed and surrounded by the connective tissue framework." It is difficult to accept this explanation, since necrosis is extremely rare in any stage of Laennec cirrhosis, and moreover, as Mallory [14] pointed out years ago, when central necrosis is present, the injury of the liver cells does not lead to proliferation of fibroblasts. Mallory's observation was reemphasized in 1934 by Rabl.[38] Connor's [39] hypothesis is ingenious. He has expressed the belief that:

> . . . fat operates mechanically, causing collapse of the sinusoids and pressure on the peripheral cells. Consequently there is anoxia of the parenchymal cells with atrophy and in acute cases a fatty necrosis. The proliferation of connective tissue cells begins in the sinusoids near the periphery of the lobule. Even though conspicuous in the portal spaces, the connective tissue does not grow out of them. A delicate reticulum forms around the degenerated parenchymal cells. This is followed by multiplication of fibroblasts. Fibrous strands are formed which connect collapsed sinusoids, and communicate with the portal spaces.

Rössle's theory of "serous hepatitis" as the fundamental background for the new formation of connective tissue is not valid since Keschner and Klemperer [40] have shown that "serous hepatitis" is associated with too many other conditions.

The series of events I have set forth thus far, namely, inflammatory cell reaction, capillarization, granuloma formation and sclerosis, is not peculiar to Laennec cirrhosis. It occurs in other types of fibrosis of the liver, although the stimulus, the origin and the distribution are somewhat different. The same sequence of events occurs in organization of thrombi.[41] The descriptions of Gross [42] and Gross and Friedberg [43]

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37. Kretz, R.: Internat. Clin. **3**:289, 1905.
38. Rabl, R.: Virchows Arch. f. path. Anat. **294**:611, 1934-1935.
39. Connor, C. L.: Am. J. Path. **13**:569, 1943.
40. Keschner, H. W., and Klemperer, P.: Arch. Path. **22**:583, 1936.
41. Heuking, E., and Thoma, R.: Virchows Arch. f. path. Anat. **109**:288, 1887. Benda, C., in Henke, F., and Lubarsch, O.: Handbuch der speziellen Pathologie und Histologie, Berlin, Julius Springer, 1930, vol. 2. Brown, G. E.; Allen, E. V., and Mahorner, H. R.: Thromboangiitis Obliterans, Philadelphia, W. B. Saunders Company, 1928. Adami.[34a]
42. Gross, L.: Am. Heart J. **13**:275, 1937.
43. Gross, L., and Friedberg, C.: Am. J. Path. **12**:4, 1936.

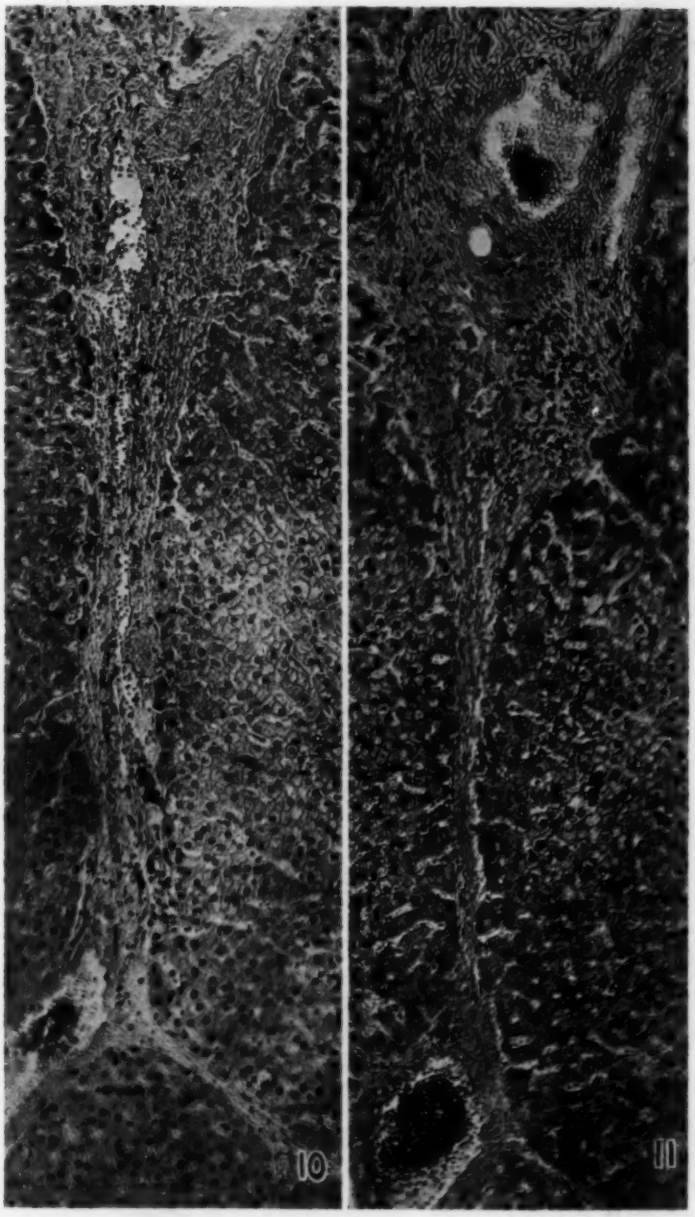


Fig. 10.—A newly formed communication between a portal vein and a hepatic vein.

Fig. 11.—The same communication appearing as a solid cord in serial section.

of the process of vascularization of the cardiac valves and verrucae in active rheumatic fever leaves no doubt in my mind that the sequence of events is that which I have described, although they did not pursue the further evolution to the sclerotic stage. They described the inflammatory cell infiltration and the capillarization of these areas and the formation of granulation tissue, the collagenization and the eventual development of a number of vessels of the musculoelastic type. Von Glahn and Pappenheimer,[44] in their report of the specific lesions occurring in the peripheral blood vessels in rheumatic fever, described vascularization occurring within areas infiltrated by round cells, plasma cells and occasional polymorphonuclears. Indeed, the subject of chronic inflammatory round cell reaction and sclerosis of tissues requires reinvestigation from this biologic point of view.

STAGE 5. INTRAHEPATIC COLLATERAL CIRCULATION

I have already described the capillarization newly found between the portal areas and the hepatic veins, so that some of the blood is short circuited, not passing through the intact sinusoids. In the maturer phases of Laennec cirrhosis, each of these bivenous strands is occupied by a venule of much larger diameter, or the entire strand may be converted into a comparatively large venule (fig. 10). Many such strands that appear purely fibrous can be demonstrated by serial sections to consist in part of the wall of a venule (fig. 11). In addition, delicate venous sprouts may be noted springing from a portal venule in one of the strands of granulation tissue and penetrating directly through the lobule into a small hepatic vein (fig. 12). Finally, there are thin-walled new capillaries that penetrate and bisect a lobule between strands of granulation tissue (fig. 13). These evidences of angiogenesis establishing a shunt between portal and hepatic veins are not seen except in the maturer phases of Laennec cirrhosis and may be interpreted as attempts to form an intrahepatic anastomosis to compensate for the distortion and narrowing of the vascular content of the liver.[45] In other words, a minor form of Eck fistula is established. This was the conclusion previously reached by MacIndoe on injecting the blood vessels of livers presenting advanced cirrhosis.

Sabourin [46] was the first to insist that in Laennec cirrhosis an intrahepatic collateral circulation existed between the portal vein and the hepatic artery. This was contested by a number of subsequent observers,

44. Von Glahn, W. C., and Pappenheimer, A.: Am. J. Path. **2**:235, 1926.

45. (*a*) McIndoe, H.: Arch. Path. **5**:23, 1928. (*b*) Herrick, F. C.: J. Exper. Med. **9**:93, 1907.

46. Sabourin, C.: Recherches sur l'anatomie normale et pathologique de la glande biliare de l'homme, Paris, F. Alcan, 1885.

but to my mind there is now sufficient corroborative evidence for the acceptance of his view.[47]

STAGE 6. REGENERATION

Liver Parenchyma.—The regeneration of intact portions of hepatic parenchyma, with the formation of adenoma-like nodules, has been repeatedly emphasized [48] and need not be reviewed here.

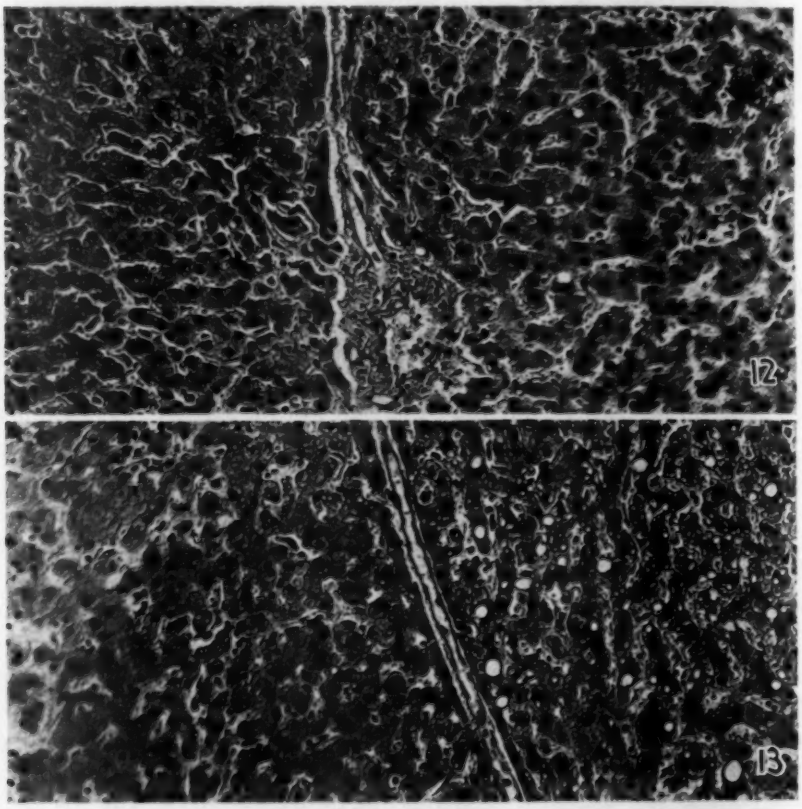


Fig. 12.—A newly formed capillary arising in a strand of granulation tissue and emptying into a hepatic vein.

Fig. 13.—A newly formed capillary bisecting a hepatic lobule.

Bile Canaliculi.—Of greater interest, because their origin has been controversial, are the bile ducts regenerated in the form of bile canaliculi, which are such a conspicuous feature in all varieties of hepatic fibrosis, including Laennec cirrhosis. Much of the disparity in the interpre-

47. Epplen, F.: Arch. Int. Med. **29**:482, 1922. Kretz.[87]

48. Karsner, H. T.: Am. J. Clin. Path. **13**:569, 1943. Rössle.[1b] MacCallum.[1e] Kretz. [87]

tations of their origin arises from the fact that most observers presume that these bile canaliculi are unitary in origin. I find three types of bile canaliculi. The first type appears early, being already visible in the fatty stage of cirrhosis, embedded in the periportal areas of fibrosis. In the later stages they are particularly abundant. As a rule, they possess no visible lumen, and serial sections have not revealed that they communicate with the bile ducts. I believe, therefore, that they represent groups of isolated portions of liver cords that have reverted to their embryonal status. Frequently one can observe a hepatic cord one end of which has been converted into a bile canaliculus (fig. 14). This has been interpreted by some [49] as evidence that hepatic cells regenerate from previously formed bile ducts, but I believe available evidence is against this interpretation. First, Herxheimer [50] showed that the cells of these bile canaliculi contain not only lipoid and hyaline substances but also intracellular bile capillaries or even masses of bile. Lucke,[49a] however, suggested that these proliferating bile ducts may have regained a compensatory capacity to metabolize bile. Second, serial sections show no communication between these new bile ducts and preformed bile ducts. Charcot and Gombault,[51] Brieger [52] and Gerhardt [53] suggested that this type of bile canaliculus is the result of increased pressure, and there are a number of observations that support this view: (*a*) These bile canaliculi make an early appearance where the intracapsular tension is increased by the fatty deposit. The effect of pressure is suggested by their situation close to the margin of the portal space and parallel to it (fig. 15). In this situation the external resistance is presumably higher because of the rigid connective tissue wall. (*b*) Newly formed bile canaliculi are numerous in the connective tissue surrounding the dilated phlebosclerotic hepatic veins in conditions associated with prolonged heightened venous pressure [54] (fig. 16). In some instances of marked hepatic venous congestion, bile canaliculi may be found along the margin of the portal space, where the external resistance is presumably increased (fig. 17). (*d*) These canaliculi may be noted just beyond the wall of a congenital cyst of the liver (fig. 18). (*e*) They are sometimes present within a slowly growing neoplasm (fig.

49. (*a*) Lucke, B.: Am. J. Path. **20**:471, 1944. (*b*) MacCallum.[1e]

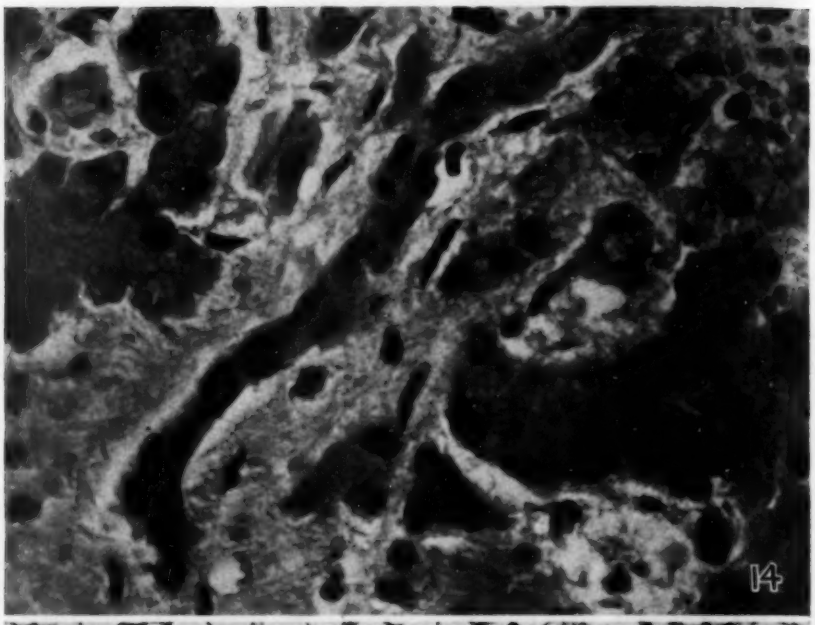
50. Herxheimer, G., and Tholldte, M., in Henke, F., and Lubarsch, O.: Handbuch der speziellen Pathologie und Histologie, Berlin, Julius Springer, 1930, vol. 5.

51. Charcot, J. M., and Gombault, M.: Arch. de physiol., norm. et. path. **3**:272, 1876.

52. Brieger, L.: Virchows Arch. f. path. Anat., **75**:85, 1879.

53. Gerhardt, cited by McMahon, Lawrence and Maddock.[58]

54. Moschcowitz, E.: Phlebosclerosis of the Hepatic Veins, in Contribution to the Medical Sciences in Honor of Dr. Emanuel Libman, New York, International Press, 1932, vol. 2, p. 857.



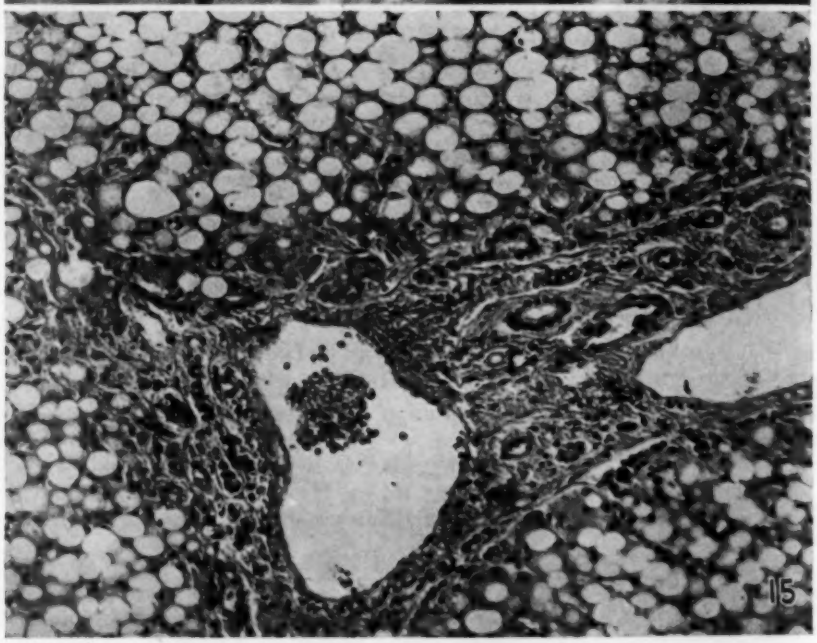


Fig. 14.—A liver trabecula being transformed into a bile canaliculus.

Fig. 15.—A small portal space in a fatty liver showing new bile canaliculi on the periphery of the space and parallel to the margins.

19). (*f*) Such bile canaliculi may be found just beneath the capsule of a liver that has been compressed by an abnormal rib (fig. 20). (*g*) Highly suggestive of the possibility that they represent the effects of pressure and an embryonal reversion is the report of Bloom [55] on the embryogenesis of human bile capillaries:

There are no evidences of hepatic ducts until the mesenchyma has penetrated the hepatic pulp along with the portal vein and its branches; then those liver cells

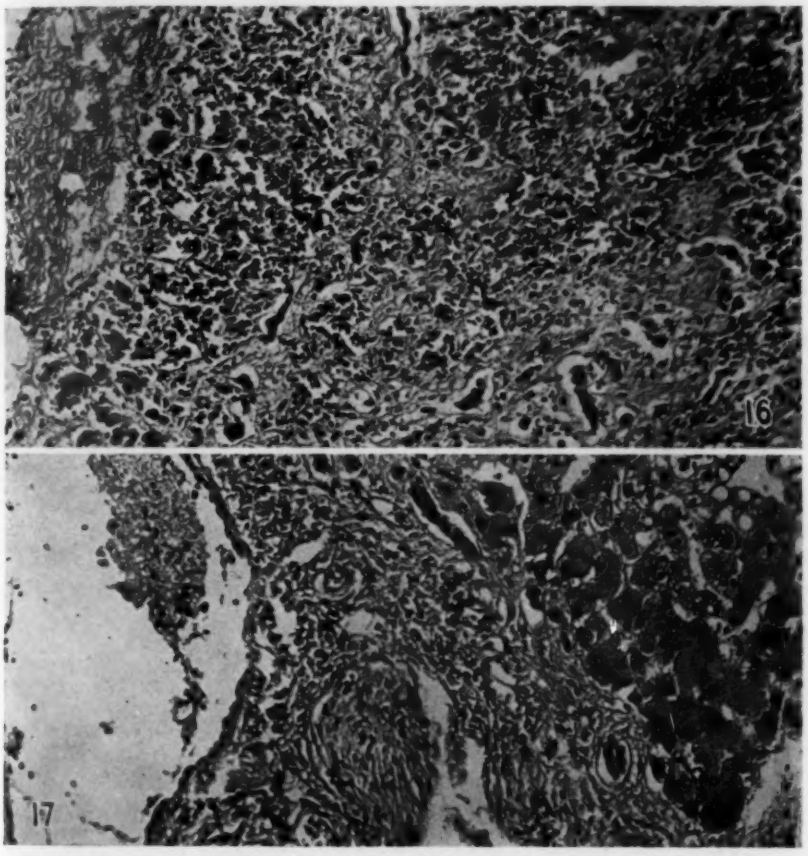


Fig. 16.—New bile canaliculi around the wall of a sclerotic hepatic vein.

Fig. 17.—A portal space in a liver in which marked venous congestion had resulted from disease of the mitral and tricuspid valves of the heart, showing new bile canaliculi along its margin.

adjacent to the mesenchyma become cuboidal; when the mesenchyma has surrounded the liver cord completely the cord will have changed its appearance so that it has the characteristics of a bile duct.

55. Bloom, W.: Am. J. Anat. **36**:451, 1926.

This observation was precisely duplicated by Doljanski and Roulet [56] on tissue culture. They cultured hepatic epithelium and mesenchyme together and found that the mesenchyme penetrated the epithelial trabeculae, and eventually, when it surrounded a group of hepatic cords, a typical bile canaliculus was formed (fig. 21).

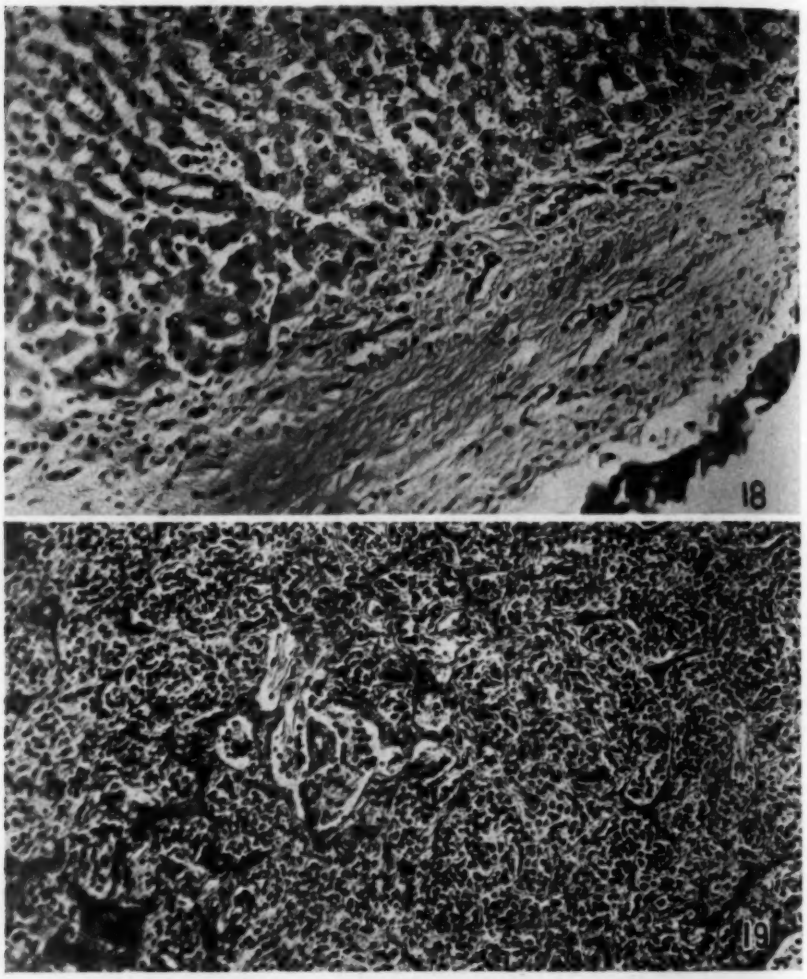


Fig. 18.—New bile canaliculi along the wall of a bile cyst of the liver.

Fig. 19.—Metastatic neuroblastoma of a liver, showing new bile canaliculi due to neoplastic compression.

The second type of bile canaliculus is observed only in the mature phase of Laennec cirrhosis and in serial sections is represented by delicate sprouts which arise from the connective tissue septums and pene-

56. Doljanski, L., and Roulet, F.: Virchows Arch. f. path. Anat. **292**:256, 1934.

trate for considerable distances, treelike, throughout the lobule, in which they end blindly. These have a delicate basement membrane and possess no lumen. They are usually accompanied by delicate, newly formed capillaries (fig. 22), but they may occur without these

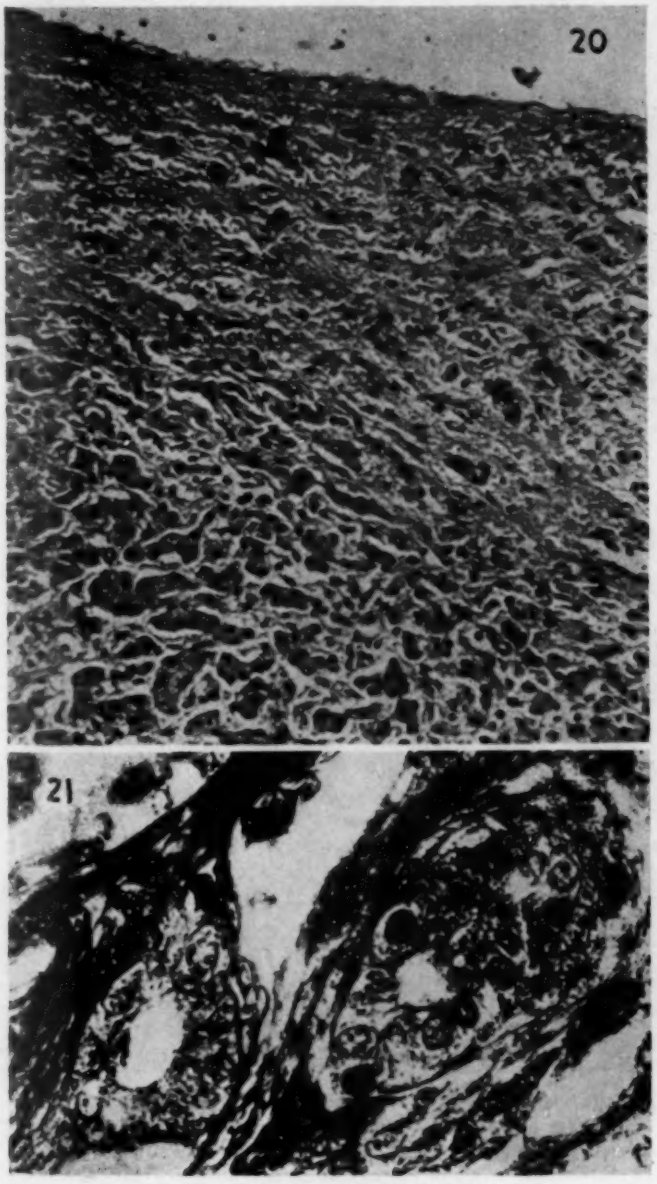


Fig. 20.—New bile canaliculi beneath the capsule of a "corset" liver.

Fig. 21.—New bile canaliculi formed in tissue culture (from Doljanski and Roulet [56]).

(fig. 23). Whether these canaliculi arise from preformed bile ducts or newly formed canaliculi I could not determine. In the terminal phases of Laennec cirrhosis they acquire a firm connective tissue mantel

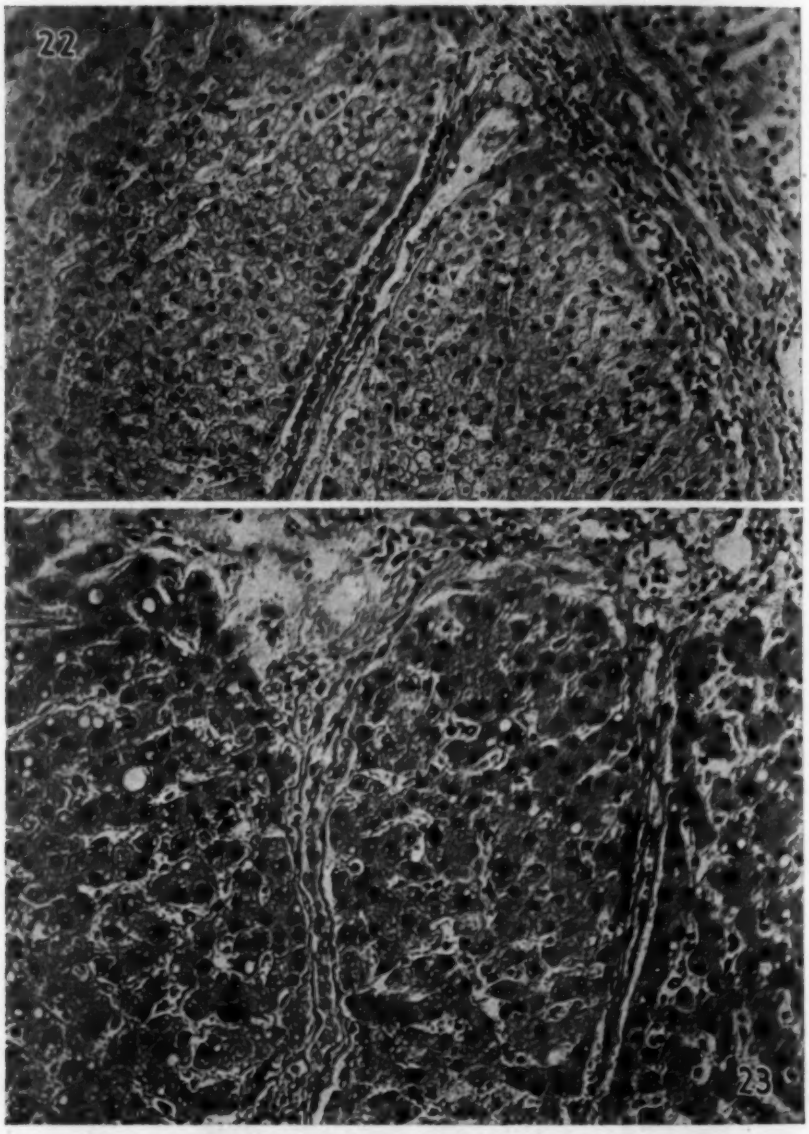


Fig. 22.—A bile canaliculus accompanied by a new capillary penetrating a hepatic lobule.

Fig. 23.—A bile canaliculus and a newly formed capillary penetrating a lobule separately.

surrounded by two or more fine capillaries (fig. 24). More often these bile canaliculi penetrate into the granulomatous septums that commu-

nicate between the affected portal spaces or between the portal spaces and the hepatic veins. This accounts for their occurrence adjacent to, or within the walls of, the hepatic or the sublobular veins.

The third type of bile canaliculus is comparatively large and at least in part of its course possesses a lumen. By serial section bile canaliculi of this type can be demonstrated as arising from the preformed bile ducts within the portal space. They penetrate into the parenchyma for variable distances, pursuing an irregular twisting course, and, like the second type, end blindly within the parenchyma. These canaliculi, also, possess a delicate basement membrane; thus far I have not noted any bile within the lumen. This type is particularly common in biliary cirrhosis (figs. 25 and 26).

The recognition of these three types helps explain why some investigators have succeeded in injecting some of the bile canaliculi [57] while others have failed. The third type probably can be injected, and McMahon and Lawrence injected them successfully in biliary cirrhosis.[58] Possibly the second type are injectible; the first cannot be injected, because they have no connection with other ducts.

The three types represent different modes of an attempt to revert to the embryonal type of liver, but in cirrhosis the process ends there, since no evidence has been found that these bile canaliculi proliferate into liver cells.

Capillaries.—There is a curious evidence of regeneration that as far as I am aware has not been reported and is independent of the early granulomatous angiogenesis that I have described. I refer to delicate capillaries that arise from venules in the connective tissue strands and that penetrate for long distances into the hepatic parenchyma. They may arise alone, but usually they accompany the fine bile canaliculi that I have described as type 2 (fig. 27). In serial sections they often terminate in what appears to be the central vein. One may only speculate on their significance, but that tney apparently represent regeneration to compensate for the diminished blood supply of the remaining portion of the hepatic lobule seems probable.

The various attempts that have been enumerated here to restore the vasculature damaged in Laennec cirrhosis fall short of complete achievement, since a considerable resistance, with establishment of portal hypertension, is maintained. This was shown by McIndoe [45a] and by the experimental investigations of Herrick [45b] and Dock.[59] Clinically it is manifest in the formation of an extrahepatic collateral circulation and especially in the invariable production of "congestive splenomegaly,"

57. Ackerman, C.: Die pathologischen Bindgewebsneubildung in der Leber und Pflügers teleologisches Causalgesetz, Berlin, C. G. Lüderitz, 1894.

58. McMahon, H.; Lawrence, J. S., and Maddock, S. J.: Am. J. Path. **5**:631, 1929.

59. Dock, W.: Tr. A. Am. Physicians **57**:302, 1942.

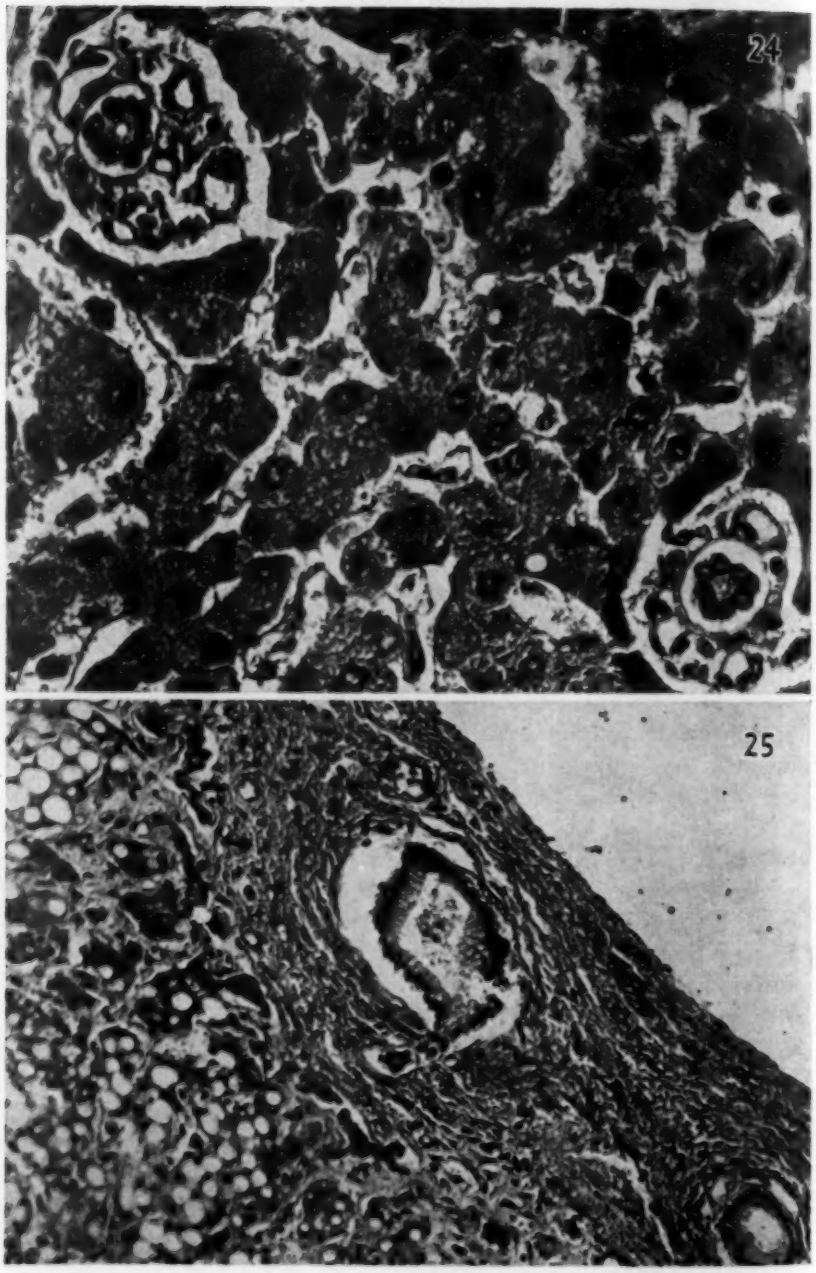


Fig. 24.—Bile canaliculi within hepatic parenchyma surrounded by new capillaries.

Fig. 25.—Portal space showing a preformed bile duct which is beginning to penetrate the parenchyma.

which, as I have tried to show,[60] is the result of portal hypertension. McIndoe [45] has shown that the task of supplying blood to the parenchyma is relegated to the hepatic artery, and this is precisely what occurs

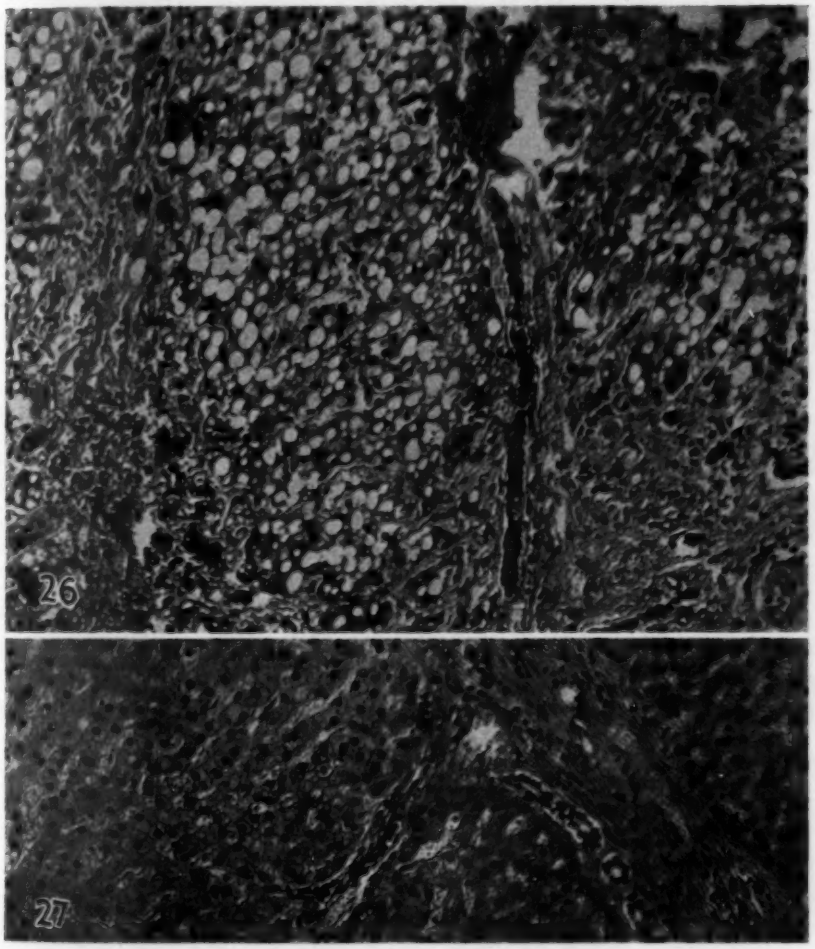


Fig. 26.—A serial section of the liver shown in figure 25 which reveals that the bile canaliculus is now in the parenchyma.

Fig. 27.—Newly formed capillaries which are branching and penetrating the lobule from a strand of granulation tissue.

after an Eck fistula. When the blood circulating through the hepatic artery fails, the patient dies of hepatic insufficiency.

60. Moschcowitz, E.: The Pathogenesis of the Splenomegaly in Hypertension of the Portal Circulation, to be published.

SUMMARY

A study of the histogenesis of Laennec cirrhosis was made from the biologic point of view and with the aid of serial sections. There is every evidence that the earliest stage of Laennec cirrhosis is invariably that represented in a fatty liver. The experimental production of fatty liver and its transformation to cirrhosis may be caused by the interaction of a nutritional deficiency and a deficiency of lipotropic factors. The precise mechanism is not clear. There is evidence that in all cases fatty liver, no matter what its origin, if given sufficient time and the continuance of the factors that produce it, will eventually transform into Laennec cirrhosis. If a proper diet is instituted, the fat eventually becomes more or less depleted, but this does not necessarily prevent the cirrhotic process from continuing, at least for a certain period. Under favorable conditions, the cirrhotic process may cease, and the end result is "latent cirrhosis." The first evidence of beginning cirrhosis is an inflammatory reaction, with round cells, monocytes, plasma cells and a few polymorphonuclear leukocytes infiltrating the periportal spaces. This is the exudative phase. The origin of the cells is discussed. These infiltrations are situated in the periportal spaces between the connective tissue stroma and the adjacent liver cords and there is a special predilection for their occurrence at the angles of the portal spaces where the interlobular vessels arise. They may also be seen similarly placed around some of the hepatic veins. The succeeding phase is a productive one and is represented by a fibroblastic transformation. The third phase is the formation of a capillary network in these areas. The capillaries are produced autochthonously by a conversion of these inflammatory cells through an angioblastic process that is precisely similar to that observed in embryonic angiogenesis. The entire process now resembles a typical aseptic cellular granulation tissue, with fibroblasts, plasma cells, polyblasts, etc. The further development of these capillaries proceeds according to the laws of Thoma. Many of the capillaries collapse, and the resulting cells evolute into progressive fibrosis and ultimately sclerosis. Other capillaries maintain their integrity and, according to the laws of Thoma, lengthen and enlarge and serve as the main blood supply of the granulomatous and fibrous strands. Serial section shows that these vessels communicate with the portal veins. No evidence is found of an arterial supply of these strands. Evidence has been submitted that this further evolution is similar to that which occurs in the embryo and in granulation tissue. These granulomatous areas at first penetrate into the interlobular septal spaces or into the lobule and unite with similar adjacent projections from other portal spaces. Often they unite with projections from the hepatic veins, partially converting the blood supply of the liver as in an Eck fistula. These have been termed bivenous strands. This

distribution forms the typical pattern in Laennec cirrhosis and accounts for the eccentricity of the central vein, the periportal distribution of the fibrosis, the distorted lobular pattern and the inclusion of the hepatic veins within the strands of connective tissue. The progressive sclerosis and its elastic transformation convert the liver from a hypertrophic to an atrophic one. In this interpretation the connective tissue structure is the result of the multipotential properties of the cells of the adult mesenchyma, which maintain in a large measure their embryonic potentialities. There is no evidence that the new connective tissue is the direct result of necrosis or of serous hepatitis. Analogous examples of angiogenesis occurring in other tissues have been cited. There is definite morphologic evidence of an intrahepatic collateral circulation. Evidences of regeneration in addition to those previously recognized have been submitted. The newly formed bile canaliculi are not explainable on a unitary basis. There are three types. Liver cells have not been seen to proliferate from any of these types. Another evidence of vascular regeneration is noted in newly formed capillaries with a delicate basement membrane that penetrate the lobule from the periportal strands for considerable distances and terminate in the central vein. These may or may not be accompanied by newly formed bile canaliculi.

STATISTICAL AND HISTOLOGIC STUDY OF ONE HUNDRED AND TWENTY CANINE NEOPLASMS

R. M. MULLIGAN, M.D.
DENVER

IN THE past three years 120 neoplasms occurring spontaneously in 98 dogs have been studied in this laboratory. The purposes of this paper are to summarize the data regarding sex, age and breed of dogs, type and location of neoplasms, and number of neoplasms per dog, and to give brief pertinent comment about the histopathologic features of several of the types described.

MATERIALS AND METHODS

The great majority of the neoplasms studied were submitted for diagnosis by Dr. L. R. Phillips, who obtained them in veterinary practice in Denver. Most of the specimens were removed in the course of surgical treatment; in some of the surgical cases information gained at autopsy was available later. The tissues were fixed in 4 per cent formaldehyde solution, trimmed, washed, dehydrated and cleared in dioxane, embedded in paraffin, cut at 8 microns of thickness, and stained with hematoxylin and eosin or with other stains as indicated.

SEX AND AGE OF DOGS

The data concerning sex and age have been summarized in table 1. The figures with respect to age agreed rather well with those of Antoine, Liégeois and Verstraete,[1] which have been summarized in a recent paper.[2]

TABLE 1.—*Age of 98 Dogs (50 Males and 48 Females)*

Years	Dogs
Under 1	2
1 - 2	6
3 - 4	7
5 - 6	6
7 - 8	12
9 -10	27
11 -12	18
13 -14	16
15 -18	4

From the Department of Pathology, University of Colorado School of Medicine.

1. Antoine, Liégeois and Verstraete: Bull. Acad. roy. de méd. de belgique **14**:301, 1934.

2. Mulligan, R. M.: Arch. Path. **38**:115, 1944.

BREED

The breeds represented in the 98 dogs with tumors have been indicated in table 2.

TYPES OF NEOPLASMS

Among the 120 neoplasms studied, 54 were cancerous and 66 were noncancerous. The various types and subtypes have been listed in table 3.

TABLE 2.—*Breed of 98 Dogs*

Terrier		45
Boston	15	
Fox	11	
Scotch	6	
Wire-haired	5	
Mongrel	3	
Airedale	2	
Wire-haired fox	1	
American bull	1	
Toy fox	1	
Shepherd		15
German	7	
Unspecified	5	
Toy	3	
Spaniel		12
Cocker	10	
English springer	2	
Collie		3
Chihuahua		3
Pekingese		3
English setter		2
German boxer		2
Belgian sheep dog		1
Dachshund		1
Labrador retriever		1
Fox hound		1
Poodle		1
Llewellin setter		1
Great Dane		1
Dalmatian		1
Chow		1
Samoyed		1
Doberman pinscher		1
English pointer		1
Saint Bernard		1

LOCATION OF NEOPLASMS

In table 4 have been noted the sites at which the 120 neoplasms were found.

NUMBER OF NEOPLASMS PER DOG

Of 98 dogs with 120 neoplasms observed, 83 had 1 neoplasm each, 9 had 2 neoplasms each, 5 had 3 each, and 1 had 4. Multiple primary tumors of the same or of different types are apparently much more common in dogs than a recent review [3] would indicate. That paper [3] stated that 46 dogs described in the literature were observed to have 123 primary tumors. The number of tumors per dog varied between 1 and 6, but 32 of the 46 dogs were afflicted with either 2 or 3 neo-

3. Mulligan, R. M.: Cancer Research **4**:505, 1944.

plasms each. The cases of multiple tumors, either identical or different in type, in the present series will be briefly detailed as follows:

Case 1 (female fox terrier, 13 years old): (*a*) mast cell sarcoma of the left flank with metastases in the left inguinal lymph nodes and (*b*) sebaceous adenoma of the right posterior cervical region.

Case 2 (female cocker spaniel, 7 years old): (*a*) mixed tumor (chondrofibroadenoma) of the right first mammary gland and (*b*) fibroadenoma of an aberrant left axillary mammary gland.

TABLE 3.—*Classification of 120 Canine Neoplasms*

Cancers		54
Sarcoma		24
Lymphosarcoma	9	
Mast cell sarcoma	9	
Fibrosarcoma	2	
Neurofibrosarcoma	2	
Chondrosarcoma	1	
Lymphangiosarcoma	1	
Carcinoma		24
Squamous cell carcinoma	7	
Basal cell carcinoma	5	
Medullary carcinoma	5	
Adenocarcinoma	4	
Sebaceous gland carcinoma	2	
Interstitial cell carcinoma	1	
Seminoma		4
Cancerous melanoma		2
Noncancerous neoplasms		66
Adenoma		28
Sebaceous adenoma	12	
Adenoma	10	
Fibroadenoma	5	
Cystadenoma	1	
Papilloma		12
Verruca vulgaris	5	
Fibroepithelioma	4	
Squamous papilloma	2	
Intraductal papilloma	1	
Mixed tumor		9
Melanoma		7
Lipoma		3
Fibroma		2
Neurofibroma		2
Myxoma		2
Epidermal cyst		1

Case 3 (female shepherd dog, 13 years old): (*a*) squamous cell carcinoma and (*b*) fibroadenoma of the right fifth mammary gland and (*c*) mixed tumor (osteochondrofibroadenoma) of the left first mammary gland.

Case 4 (female fox terrier, 12 years old): (*a*) fibroadenoma and (*b*) cystadenoma of a fourth mammary gland.

Case 5 (male Airedale terrier, 9 years old): (*a*) myxoma of the right ventral abdominal region and (*b*) sebaceous gland carcinoma of the lumbar region.

Case 6 (female Chihuahua, 12 years old): (*a*) mixed tumor (adenofibrochondro-osteoma) of the left fifth mammary gland and (*b*) mixed tumor (adenochondrofibroma) of the right third mammary gland and (*c*) mixed tumor (chondrofibroadenoma) of the right fourth mammary gland.

Case 7 (male Pekingese, 9 years old): (*a*) seminoma and (*b*) tubular adenoma of the left testis.

Case 8 (female fox terrier, 13 years old): three sebaceous adenomas of the trunk.

Case 9 (female Chihuahua, 9 years old): two cutaneous melanomas at sites not specified, but representative of multiple similar cutaneous tumors found at autopsy.

Case 10 (male Airedale terrier, 14 years old): (*a*) cancerous melanoma of the right buccal region, (*b*) melanoma of the ventrum of the tail, which was like other dark brown tumors on the tail, and (*c*) fibroepithelioma of the right ventral abdominal region.

Case 11 (male Doberman pinscher, 12½ years old): (*a*) carcinoma of a perianal gland and (*b*) two adenomas of perianal glands.

Case 12 (male Scotch terrier, 6 years old): basal cell carcinomas of (*a*) the right labial region and (*b*) the right brachial region.

TABLE 4.—*Location of 120 Neoplasms*

Skin		46
Extremities	16	
Head	12	
Thorax	8	
Abdomen	4	
Neck	2	
Unspecified	2	
External genitalia	1	
Tail	1	
Subcutaneous tissue		24
Extremities	7	
Thorax	5	
Abdomen	4	
External genitalia	3	
Head	2	
Neck	2	
Tail	1	
Mammary glands		23
First	3	
Second	2	
Third	2	
Fourth	10	
Fifth	4	
Aberrant axillary	2	
Perianal glands		11
Testes		6
Lymph nodes		3
Harder's gland		1
Hard palate		1
Vagina		1
Vulva		1
Retroperitoneum		1
Gum		1
Unspecified		1

Case 13 (male German shepherd dog, 14 years old): (*a*) melanoma of the left metacarpus and (*b*) sebaceous adenomas of the dorsal cervical, left thoracic and left temporal regions.

Case 14 (female Boston terrier, 9 years old): (*a*) mast cell sarcoma of the right side of the vulva and (*b*) melanoma of the right hock.

Case 15 (female cocker spaniel, 5 years old): two adenomas of the perianal glands.

COMMENT ON SEVERAL TYPES OF NEOPLASMS

Sarcoma.—Of the 9 lymphosarcomas, 8 were composed mainly of lymphoblasts and 1 of lymphocytes. Five involved the skin, 3 the lymph

nodes, and 1 the subcutaneous tissue of the scrotum. The 5 in the skin were difficult to understand when the clinical course was compared with the histologic character of the neoplasm. These 5 tumors occurred in a male Boston terrier 1 year old and 4 cocker spaniels (a female 3½ months old, a male 1 year old, a female 15 months old and a female 5 years old). The neoplasms involved the right thoracic region, the left anterior phalanges, the left carpus, the right axilla and the left external auditory meatus, respectively. They varied between 8 and 20 mm. in greatest diameter, were not of congenital origin, grew rapidly in the several weeks before excision and have not recurred in two months to two years of observation. Histologically, the tumors were indistinguishable from lymphosarcoma of the lymphoblastic type. The constituent cells infiltrated irregularly through the dermis and upper hypodermis, were crowded around accessory structures of the skin and spread apart collagenous connective tissue bundles. The cytoplasm of the cells was fairly defined, the nuclei were large and rounded, the chromatin net was finely divided, one or more nucleoli were visible, and mitotic figures varied in frequency. Giemsa stain showed an absence of specific granulation, and Foot's modification of the Maresh-Bielschowsky stain for reticulum fibrils did not indicate that such fibrils were formed directly from the neoplastic cells. Rather the reticulum fibrils present were in relation to the infiltrated stroma. Extragenital venereal sarcoma could be ruled out, since venereal sarcoma in the usual genital location has not been noted in the canine tissues submitted to this laboratory for diagnosis. In the hundreds of both male and female dogs observed in the laboratories here in the past eight years, venereal sarcoma has not been seen once. Whether these 5 cutaneous lesions were noncancerous and of some unknown viral origin or represented a cutaneous expression of a later-blossoming diffuse lymphoid disease could not be determined. The only comparable group found mentioned in the literature was one of 60 occurring in dogs, reported by Auler and Wernicke [4] under the diagnosis of "benign round cell sarcoma," who described this tumor as circular, flat, smooth, hairless, firm, light red, occurring as a nodule in the cutis, never growing larger than 25 mm. in diameter, never forming metastases and observed nearly always in young dogs that were more than 6 months of age. Local cautery and excision resulted in complete cure in all 60 cases.

The 3 dogs with lymphosarcoma of lymph nodes included: a Boston terrier, 9 years old, female, with lymphoblastic lymphosarcoma in the cervical, inguinal, tracheal, mediastinal and mesenteric nodes, the spleen, the liver, the bone marrow, the lungs and ectopic tracheal bone marrow; a Scotch terrier, 9, male, with lymphoblastic lymphosarcoma in the cervical, mediastinal and mesenteric lymph nodes, the spleen, the liver

4. Auler, H., and Wernicke: Ztschr. f. Krebsforsch. **35**:1, 1931.

and the lungs; a Scotch terrier, 9, male, with lymphocytic lymphosarcoma in the cervical, inguinal, tracheal, mediastinal and mesenteric lymph nodes, the spleen, the liver, the bone marrow, the gallbladder, the stomach, the kidneys, the lungs and the thyroid and parathyroid glands. Another dog with lymphoblastic lymphosarcoma was a Boston terrier, 8 years old, with a subcutaneous lesion in the scrotum. The involved lymph nodes showed their structure fairly uniformly obliterated by proliferated lymphoblasts or lymphocytes, as the case might be. The lymphoid nodules in the spleen were enlarged by increase of the same cells, which spilled out into surrounding sinusoids, with frequent fusion of several adjacent nodules. The conglomerations of altered lymphoid tissue thus produced were much more irregularly distributed and larger than those noted in nodular hyperplasia of lymphoid follicles,[3] common in old dogs. In the liver the lymphoid proliferation was distributed chiefly in the periportal areas. The bone marrow showed the usual myeloid and erythroid elements diffusely replaced by a monotonous type of cells, either lymphoblasts or lymphocytes. The lungs revealed specific involvement of preexisting lymphoid nodules. In no instance was the level of blood leukocytes unusually elevated, nor were abnormal cells noted in the peripheral blood during life. Bloom and Meyer[5] have recently described 13 cases of canine lymphosarcoma under the term "malignant lymphoma." They were able to separate lymphocytic, lymphoblastic and polymorphous types and emphasized the fact that the peripheral blood was not invaded by specific cells.

The 9 mast cell sarcomas occurred in the dog concerned in case 1 of multiple tumors (described on page 218), a 9 year old female Boston terrier with multiple lesions of the left hindleg and the inguinal region, a 3 year old female German boxer with a tumor of the nipple of the left fourth mammary gland, a 4½ year old female English setter with a neoplasm of the right tarsus, a 12 year old male fox terrier with a lesion of the left gluteal region, a 9 year old female Boston terrier with a tumor of the right side of the vulva, an 8½ year old female Boston terrier with multiple lesions of the right axilla, a 10 year old male Boston terrier with a tumor of the scrotum and a 10 year old female Boston terrier with a neoplasm of the left gluteal region. The specific cells of these lesions may show easily identified, deeply basophilic cytoplasmic granules in the routine hematoxylin and eosin–stained section, but in enough instances to be annoying this stain fails to demonstrate the specific granulation. Giemsa stain or Nissl stain may be necessary to prove the presence of these granules. The specific cells have rather abundant, clearly defined, light basophilic cytoplasm and round nuclei. The nuclei are large, have finely divided chromatin and prominent nucleoli, especially in those lesions in which the specific

5. Bloom, F., and Meyer, L. M.: Am. J. Path. **21**:683, 1945.

granulation is difficult to identify without special stains, or in recurrent lesions, in which the capacity to form these granules is lessened as the cells become more primitive. In those lesions containing cells with relatively small, condensed nuclei, the cytoplasm is usually abundantly filled with specific granules, often to the point of obscuring the nucleus. The mast cells in a mast cell sarcoma are arranged in a rather loose fashion. Sometimes in such a tumor whole low power fields reveal but few of the specific cells. In the subcutaneous tissue the connective tissue bundles are spread apart by the loose aggregates of mast cells, which also surround frequently dilated accessory structures of the skin, notably sebaceous and sweat glands. Often various leukocytes, especially segmented neutrophils and lymphocytes, are apt to confuse the diagnosis, since these inflammatory cells accompany the ulcerative process which nearly always involves the skin and accessory structures overlying or intermingled with a mast cell sarcoma. Murray [6] described 2 cases of mast cell sarcoma among 26 cases of sarcoma; in the remaining 24 cases the sarcoma was stated to be round cell (10), spindle cell (2), alveolar (2), melanotic (2), osteogenic (2), miscellaneous (4) and not typed (2). Chambers [7] reported 15 histologically confirmed cases of canine cancer, among which were 3 cases of mast cell sarcoma. In commenting on sarcoma, Chambers said:

> . . . Sarcoma of the axillary region is not uncommon. A common place to find these malignant growths is in the popliteal region, often implicating the popliteal gland. The type met with is of the mast-celled sarcoma variety. If boldly removed a favourable result may be expected, but if the smallest piece be left, recurrence will take place with great rapidity. Some of these mast-celled sarcomas are very malignant, but there are cell gradations down to practically benign growths.

Bloom [8] recorded 5 instances of mast cell sarcoma under the name "mast cell tumor" but was unaware at the time of the contributions of Murray [6] and Chambers.[7]

One fibrosarcoma was on the elbow joint of a 12 year old female Belgian sheep dog, and the other occurred in the left inguinal region of a 13½ year old female Boston terrier. The constituent cells were largely elongated spindle cells, unevenly arranged, with the anaplastic features of cancerous fibroblasts. In some areas well developed collagen fibrils, usually occurring singly between tumor cells but also in discrete bundles, were noted both with hematoxylin-eosin and with Mallory's connective tissue stain. Areas of necrosis were numerous. This relatively low incidence of spontaneous fibrosarcoma in dogs of this series contrasted strikingly with the number of tumors of this type produced in

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6. Murray, J. A., in Third Scientific Report, Imperial Cancer Research Fund, London, 1908, pp. 41-60.
7. Chambers, F.: Vet. Rec. **11**:709, 1931.
8. Bloom, F.: Arch. Path. **33**:661, 1942.

the fascia of dogs by methylcholanthrene, since fibrosarcoma so induced[9] has been the only type of neoplasm so far generated by this carcinogen in this location in dogs.

One neurofibrosarcoma was found in the cervical region of a male great Dane, 4 years old, and the other was located in the left axillary region of a female wire-haired terrier, 16 years old. In some areas these lesions showed the relatively uniform bundle-like and whorled arrangements of cells as well as the occasional nuclear palisading seen in neurofibroma, but large, fat, bizarre, heavily chromatinized nuclei, mitotic figures, large areas of necrosis and spectacular disarrangement of both tapering and stubby spindle cells indicated the cancerous nature of these neoplasms.

A male shepherd dog, 3 years old, had a chondrosarcoma on the left side of the hard palate. This neoplasm consisted of atypical mesenchymal connective tissue, including mainly tapering spindle cells, which were widely transformed into closely packed pale acidophilic polyhedral cells containing rounded nuclei with fine chromatin, prominent nucleoli and mitotic figures. The edges of the cells were bordered by intertwining dark blue ground substance, which in many areas blended with large areas of calcium deposit to the point of obliterating parts of the neoplasm. Several clearly defined areas of primitive cartilage were found. The overlying stratified squamous epithelium was diffusely and acutely ulcerated.

A lymphangiosarcoma was present at the base of the penis of a 5 year old male German shepherd dog. This tumor, grossly pale gray, consisted of many small and medium spaces; most of these were empty, but some enclosed pale acidophilic fluid and were lined by flattened endothelial cells, surrounded by masses of interlocking short spindle or polyhedral cells with heavily chromatinized oval nuclei, somewhat indistinct nucleoli and numerous mitotic figures. In several areas the spaces were uniformly small and fitted closely together in a mosaic pattern, resting in a delicate reticular stroma. The overlying epithelium was greatly thinned or was ulcerated and replaced by acutely inflamed granulation tissue.

Carcinoma.—The squamous cell carcinomas were noted in the dog concerned in case 3 of multiple tumors (described on page 3), the right lateral thoracic region of a 7 year old female English setter, the left thigh of a 14 year old male cocker spaniel, the right inguinal region of a 12 year old female fox terrier, the right fourth mammary gland of a 10 year old female toy shepherd, the anus of an 8 year old male fox terrier and the wall of an epidermal inclusion cyst of the tail of an 11½ year old male Saint Bernard. The usual features of squamous

9. Mulligan, R. M.: (*a*) Proc. Soc. Exper. Biol. & Med. **57**:134, 1944; (*b*) Exper. Med. & Surg. **4**:333, 1946.

cell carcinoma were observed, including: dedifferentiation of epidermis into nests and strands of anaplastic epithelial cells, with the layered arrangement of the more normal epidermis being preserved to some degree on either side; transdermal invasion of the hypodermis; pearl formation; pronounced acanthosis, and mitosis. Varying acute and chronic inflammatory reaction was usually noted, since ulceration was frequent.

Of the 5 basal cell carcinomas, 1 was located on the lower lip of a male German shepherd dog, 13 years old; 2 were noted in the left submaxillary regions of 2 male collies, 9 and 9½ years old, and 2 were observed in a male Scotch terrier, 6 years old, with 1 on the lower lip and 1 in the brachial region. These neoplasms apparently originated in hair follicles according to the theory of Foot[10] by which basal cell carcinoma originates in distorted primordia of dermal adnexae. The cells in these 5 tumors resembled only the basal cells of the epidermis, had no connection with the overlying epidermis, grew in slender strands or in broad sheets, displayed varying anaplasia, enclosed structures suggestive of abortive hair follicles and were surrounded by narrow bands of fibrous connective tissue with practically no inflammatory reaction.

Four of the 5 medullary carcinomas were located in the left fifth mammary gland of a 10 year old female shepherd dog, the left ischial region of a 13 year old female toy shepherd, the perianal glands of a 14 year old male shepherd, and the right second mammary gland of a 12 year old female fox terrier; the fifth was seen in case 11 of multiple tumors (described on page 219). The medullary carcinomas consisted of polyhedral epithelial cells with hazy borders and nuclei varying in size and shape or containing various numbers of mitotic figures. These cells were arranged in large solid masses and sheets in a relatively scanty connective tissue stroma. Widespread central necrosis was noted in these tumors.

The 4 adenocarcinomas were noted in the right second mammary gland of a 13 year old female Boston terrier, the right cryptorchid testis of a 7 year old male American bull terrier, the right first mammary gland of a 10 year old female English springer spaniel and the right fourth mammary gland of a 14 year old male mongrel American bull terrier. The 2 neoplasms last mentioned were papillary cystadenocarcinomas, in which neoplastic proliferation apparently began as multiple papillary growths within cysts (these being probably of ductal origin) and underwent cancerous degeneration, with formation of spaces lined by anaplastic columnar epithelial cells, which were found both within the papillary folds and in the invaded walls of the cysts. Cases of mammary neoplasms occurring in the male dog have been reported by relatively few authors, including Murray[6] (2 cases),

10. Foot, N. C.: Am. J. Path. **23**:1, 1947.

Fröhner [11] (1 case) and Baldoni [12] (5 cases). Baldoni's reports were recently summarized.[13] The adenocarcinoma of the testis consisted of cells with the morphologic aspects of anaplastic spermatogonia and primary spermatocytes. The constituent cells were arranged in palisaded and heaped-up fashion around glandular spaces of varying size, which were divided into compartments by interlacing strands of supporting stroma. The larger glandular spaces tended to be filled with more solid masses of similar neoplastic cells. Lacking in the dog with the adenocarcinoma of the testis were symptoms referable to the endocrine glands like those observed [14] in some dogs with this type of testicular neoplasm.

The 2 carcinomas of sebaceous glands were observed in case 5 of multiple tumors (described on page 218) and in a 7 year old male fox hound, which had the lesion on the left hock joint. These lesions were larger, were ulcerated, were much less differentiated toward normal sebaceous glands, definitely invaded deep into the hypodermis, clearly consisted of anaplastic cells and were distinguished by mitotic figures as compared with the sebaceous adenomas to be described in the following section.

The interstitial cell carcinoma involved the left scrotal testis of a 12 year old male Boston terrier, but no symptoms referable to the endocrine glands were noted. The tumor, grossly tan or light brown, was made up largely of big polyhedral cells with much acidophilic cytoplasm, which was frequently finely and sometimes coarsely vacuolated. The nuclei varied in size and depth of staining, were generally round and displayed a fine chromatin net and a prominent nucleolus. The cells, usually well preserved, were arranged in solid masses or slender strands on a well vascularized reticular stroma, which contained many dilated lymphatic channels and scattered macrophages containing hemosiderin.

Adenoma.—The 12 adenomas of the sebaceous type were observed in cases 1, 8 and 13 of multiple tumors (described on pages 218 and 219), and on the eyelid of an 8 year old male German shepherd dog, the temporal region of a 7 year old male cocker spaniel, the left metacarpus of a 9 year old male wire-haired fox terrier, the eyelid of a 12 year old female fox terrier, and the left stifle bone of a 14 year old male German shepherd dog. These lesions were much more definitely neoplasms than their counterpart in human subjects, since they were discrete, even proliferations of well differentiated sebaceous glands, largely confined to the dermis and the upper part of the hypodermis,

11. Fröhner: Monatsh. f. prakt. Thierh. **6**:1, 79 and 111, 1895.

12. Baldoni, A.: Mem. r. Accad. d. sc. d. Ist. d. Bologna (a) **5**:33, 1927-1928; (*b*) **10**:183, 1912-1913; **10**:37, 1922-1923; summarized by Mulligan.[13]

13. Mulligan, R. M.: Arch. Path. **39**:162, 1945.

14. Mulligan, R. M.: Am. J. Path. **20**:865, 1944.

and were bulging unequivocally beneath the greatly thinned epidermis as undoubted tumors projected above the surrounding skin.

The 9 adenomas of perianal glands affected the dogs concerned in cases 11 and 15 of multiple tumors (described on pages 219 and 220) and 5 male dogs, of which 3 were 10 years old (Boston terrier, fox terrier and poodle), 1 was 11 years old (wire-haired fox terrier) and 1 was 15 years old (toy fox terrier). These adenomas, 5 to 15 mm. in diameter, consisted of regular polyhedral cells possessing abundant acidophilic cytoplasm and central round nuclei containing fine chromatin and a discrete acidophilic nucleolus. The cells were arranged in even columns on a delicate, well vascularized reticular stroma.

The 5 fibroadenomas were observed in cases 2, 3 and 4 of multiple tumors (described on page 218) and in an aberrant right axillary mammary gland of a 10 year old female fox terrier and the right third mammary gland of a 6 year old female Scotch terrier. The cystadenoma was also seen in case 4. A tubular adenoma coexisted with a seminoma in the left scrotal testis of a 9 year old Pekingese.

Papilloma.—The 5 papillomas of the verruca vulgaris type occurred on the right posterior phalanges of a 3 year old female wire-haired terrier, the left metacarpus of a 1 year old male mongrel terrier, the ear of a 3 year old female German boxer, the prepuce of an 8 month old Dalmatian and the eyelid of a 1 year old female mongrel terrier. These lesions were like those described by DeMonbreun and Goodpasture [15] as occurring spontaneously and experimentally in the buccal cavities and on the lips of puppies and would probably have regressed spontaneously if unmolested. Oral papillomatosis has been observed in a young female dog admitted to this laboratory, but all the lesions spontaneously disappeared in two months. In dogs verruca vulgaris is due to a virus,[15] and this etiology has also been demonstrated for it in human subjects. The lesions in dogs, quite comparable to those in man, consisted in great thickening and papillary arrangement of the epidermis with piling up of the corneal layer, widening of the granular layer, elongation of rete pegs, lengthening of dermal papillae and chronic inflammatory changes of the dermis.

The 4 fibroepitheliomas affected the left carpus of a 13 year old male German shepherd dog, the left tarsus of a 6 year old female German shepherd, the left gluteal region of a 9 year old female Boston terrier and the dog concerned in case 10 of multiple tumors (described on page 219). These tumors were present in old dogs and consisted of a central, moderately vascular core of fibrous connective tissue and a frequently undulated covering of variously thickened epidermis attached to the surrounding skin by a pedicle. The 2 squamous papillomas were seen on the right metacarpus of a 10 year old female wire-haired terrier

15. DeMonbreun, W. A., and Goodpasture, E. W.: Am. J. Path. **8**:43, 1932.

and the gum of a 12 year old female collie. These lesions showed little cellular activity in the corneal and granular layers of the stratified squamous epithelium but exhibited increase of cells in the germinal or the basal cell layer, especially in the former, rare mitotic figures and some acanthosis. The lamina propria was chronically inflamed. These tumors were comparable to human senile hyperkeratosis. The intraductal papilloma involved the right fourth mammary gland of a 10 year old female Boston terrier and grew within several ducts of the gland.

Melanoma.—The 9 melanomas were noted in cases 9, 10, 13 and 14 of multiple tumors (described on pages 219 and 220) and in the right axilla of a 12 year old male Boston terrier (cancerous), an eyelid of a 12 year old female Pekingese (noncancerous) and the right metacarpus of a 2 year old Scotch terrier (noncancerous). The cells of the 7 noncancerous melanomas were either polyhedral or spindle shaped, contained much melanin and were located abundantly in the dermis and the upper part of the hypodermis. The 2 cancerous melanomas consisted mainly of polyhedral cells with various amounts of melanin pigment, often none, within the cytoplasm. Definite anaplasia of the cells included variation in size and shape, hyperchromatism of the nuclei, conspicuous nucleoli and many mitotic figures. Canine melanomas have not been described too often by others (Auler and Wernicke [4]; Murray [6]; Chambers [7]; Fölger [16]; Cohrs [17]; Feldman [18]). Passey [19] was able to produce 2 cancerous melanomas in dogs by applying tar to the skin of mongrel Airedale terriers for several years.

Mixed Tumor.—The 9 mixed tumors occurred in cases 2, 3 and 6 of multiple tumors (described on page 218) and in the right fourth mammary gland of a 7 year old female dachshund, the left Harder's gland of a 12 year old male English springer spaniel, the left fourth mammary gland of an 11 year old female Chihuahua and the right fourth mammary gland of a 7 year old female Samoyed. The fundamental mixed tumor character of many mammary neoplasms was recently discussed.[13]

Seminoma.—Four seminomas occupied scrotal testes. Three were in the left testes of a 9 year old Pekingese, an 18 year old toy shepherd dog and a 9 year old fox terrier. The fourth involved the right testis of a 16 year old chow. The toy shepherd showed metastatic seminoma in pelvic lymph nodes at autopsy eight months after excision of the primary tumor. Canine testicular neoplasms reported in the literature have been reviewed.[13]

16. Fölger, A. F.: Ergebn. d. allg. Path. u. path. Anat. **18**:372, 1917.
17. Cohrs, P.: Ztschr. f. Krebsforsch. **24**:156, 1926.
18. Feldman, W. H.: Proc. Staff Meet., Mayo Clin. **3**:253, 1928.
19. Passey, R. D.: J. Path. & Bact. **47**:349, 1938.

Other Neoplasms.—The 3 lipomas were noted in the tissue over the sternum of a 10 year old female Labrador retriever, the retroperitoneum (2,645 Gm.) of a 12 year old male Llewellin setter and the right pectoral region of a 7 year old female German shepherd dog. One of the 2 fibromas was present in the right lumbar region of a 13 year old male cocker spaniel and the other on the right anterior phalanges of a 12 year old male English pointer. The 2 myxomas were found in case 5 of multiple tumors (described on page 218) and the right cervical region (1,368 Gm.) of a 14 year old male shepherd dog. The 2 neurofibromas were seen in 2 10 year old female dogs. One was in the left gluteal region of a wire-haired terrier and the other in the vagina of a Scotch terrier. The histologic structure was quite similar to that of human neurofibroma. Five epidermal inclusion cysts were noted over the nuchal crest of a 4 year old male cocker spaniel.

SUMMARY

Of 98 dogs with 120 neoplasms, 80 were 6 years of age or older. Fifty were males and 48 were females. Eighty-three dogs had 1 tumor, 9 had 2, 5 had 3, and 1 had 4 tumors. The breed in 45 was terrier, in 15 shepherd, in 12 spaniel, in 3 collie, in 3 Pekingese and in 3 Chihuahua; the remaining 17 dogs were of miscellaneous breeds. The types of neoplasms among the 54 cancers were sarcoma in 24, carcinoma in 24, seminoma in 4 and cancerous melanoma in 2; among the 66 noncancerous tumors the types were adenoma in 28, papilloma in 12, mixed tumor in 9, melanoma in 7, lipoma in 3, fibroma in 2, neurofibroma in 2, myxoma in 2 and epidermal cyst in 1. The location of the 120 neoplasms was as follows: 46 were in skin; 24, in subcutaneous tissue; 23, in mammary glands; 11, in perianal glands; 6, in testes; 3, in lymph nodes; 7, in miscellaneous sites.

MASTITIS OF THE MOUSE AS RELATED TO POST-SECRETORY MAMMARY INVOLUTION

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MINNEAPOLIS

THE MORPHOLOGY of the mammary glands of the female mouse has received much attention in the course of many studies of spontaneous and induced tumors and of the hormonal control of mammary growth and secretion. In contrast to the great emphasis on neoplastic disease of the mammary glands of mice and other rodents, there is but little information concerning inflammatory disease of the same organs of these species. However, because of the great frequency and significance of neoplasms of the human breast it is to be expected that there would be greater interest in neoplastic than in inflammatory conditions of the mammary glands of experimental animals. In dairy animals, in which mastitis is of great economic importance, extensive studies have been made of its causation, control and treatment.

The term "mastitis" has often been used improperly to designate poorly classified lesions of the breast which have not been of definite inflammatory nature. In this report the term is limited to morphologically acute inflammatory conditions. At present it seems improbable that true mastitis has a specific etiologic relation to carcinoma of the breast. Therefore, inflammatory conditions have not been of particular interest in experimental cancer research related to the breast. In mice, some degree of inflammation has been observed in mammary glands that were chronically stimulated with mammotropic substances, particularly estrogens.[1] Inflammatory lesions occur in other organs, particularly the uterus and cervix, in which chronic hyperplasia has been induced and maintained by estrogens.[2] However, acute mastitis is usually associated

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This investigation was aided by grants made to the late Prof. Edgar Allen from the Committee for Research in Problems of Sex, of the National Research Council and by grants from the Graduate School of the University of Minnesota.

1. Gardner, W. U.: Arch. Path. **27**:138, 1939. Taylor, H. C., Jr., and Waltham, C. A.: Arch. Surg. **40**:733, 1940.

2. Gardner, W. U.: Surgery **16**:8, 1944.

with secretory rather than growth phases of the mammary cycle. The mastitis described here occurred under rather atypical conditions during postsecretory mammary involution. The inflammatory lesions were first encountered in a study of the morphologic changes which ensued subsequent to cessation of milk removal.[3] The conditions under which the disease developed should not be termed "normal." It is hoped to demonstrate that the somewhat atypical state of postsecretory mammary involution was related to the mastitis.

METHODS

Postsecretory mammary involution was studied in 114 uniparous mice of the A, CHI and NH strains of Dr. L. C. Strong. In the first two strains spontaneous mammary carcinomas occur, but at a later age than that of the animals included here. A majority of the mice were CHI's, and mastitis was limited to the CHI and NH strains. Twenty-five CHI mice were examined for mastitis at all stages of lactation (twenty-one days). When a mouse was observed to be pregnant, she was isolated and remained thereafter separated from other mice, except for her litter. The size of the suckled litters was standardized at 7 or 8 members.

Involution of the mammary parenchyma was induced by separating the mothers from their litters: (*a*) 24 mice at parturition and prior to any suckling; (*b*) 76 mice after ten days of lactation, by which time maximum secretion had been attained; (*c*) 14 mice at the end of the usual twenty-one days of lactation. Mice in these three groups (*a, b, c*) were killed at intervals of one to sixty days after separation from their litters.

Immediately subsequent to being separated from their litters, 43 mice were subjected to certain experimental procedures. Ten mice in the *a* group, described in the foregoing paragraph, were treated with prolactin (2 mg. daily) and were killed two, four, six, seven and ten days after the initiation of treatment. Thirty-three mice of the *b* group were treated as follows: Eight mice received estrone (25, 50, 100, 250, 500, 800 or 1,000 international units) daily for five days, at which time they were killed for study. Similarly 6 mice received 0.5 mg. of progesterone daily for five to seven days, and 4 mice were given 0.5 mg. of testosterone propionate daily for three, four and seven days and were then killed. All of the aforementioned substances were injected subcutaneously. Six mice which had been ovariectomized at the time of being separated from their young were killed two, five, seven, ten, twenty and thirty days later. Likewise 9 mice were hypophysectomized at the time their litters were removed and were killed one to five days after operation.

Tissues were fixed in a mixture of solution of formaldehyde U.S.P., alcohol and acetic acid (Lavdowsky's fluid), and sections were stained with hematoxylin and eosin or by the Masson trichrome or the Mallory connective tissue method.

Bacteriologic studies were made by streaking aseptically exposed mammary tissue, adjacent lymph nodes and spleen on veal infusion-agar slants. This was done with 13 mice killed at intervals of three to eight days after they had been segregated from their litters. Studies of an organism (a Pasteurella) isolated from a mastitic gland are described later. Four uniparous mice were segregated from their litters on the tenth day of lactation, and then 0.05 cc. of a veal infusion-agar slant culture of the aforementioned organism (washed with broth) was injected into the right lumbar (no. 4) mammary gland just deep to the nipple. Sterile broth

3. Williams, W. L.: Am. J. Anat. **71**:1, 1942.

was similarly injected into adjacent mammary glands. These mice were killed seven days later, and cultures were made of all mammary glands, related lymph nodes and spleen.

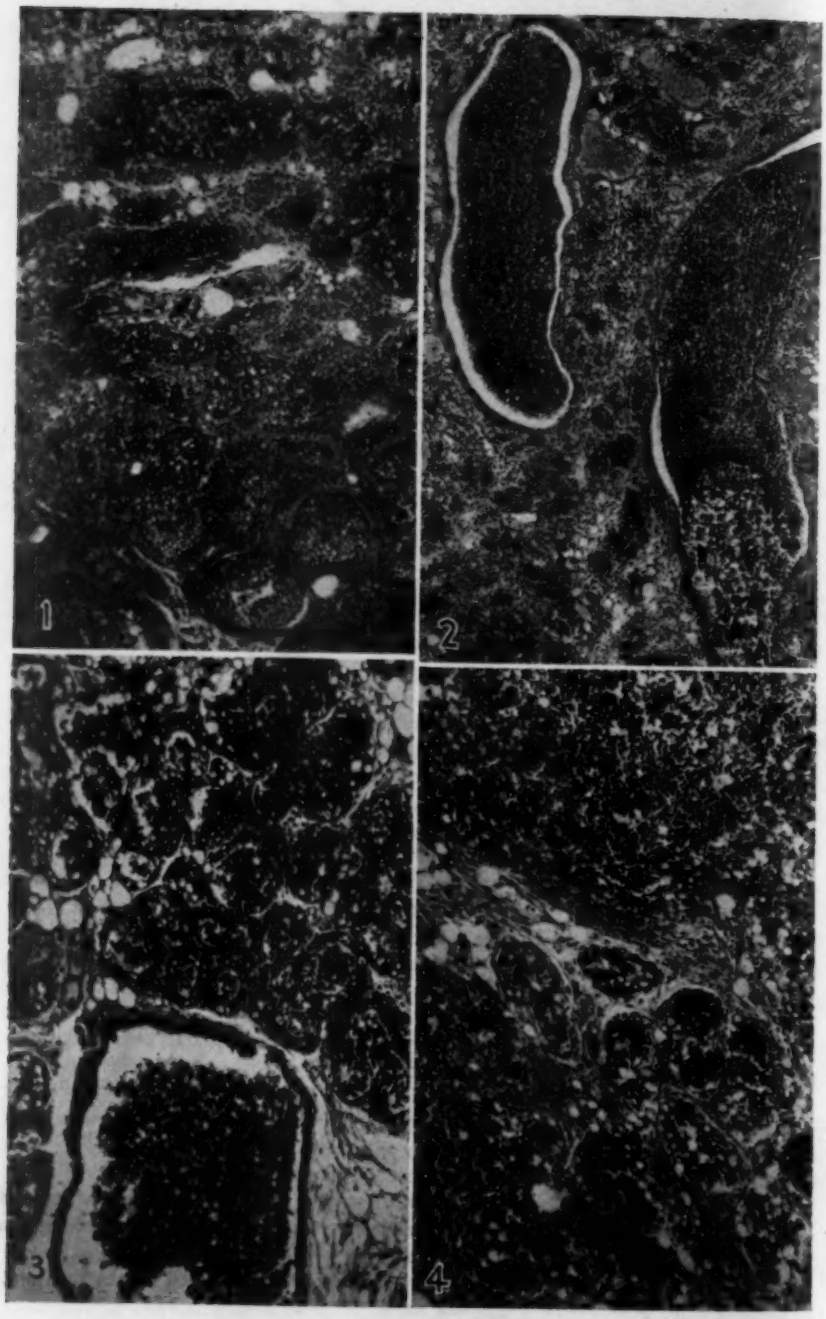
MORPHOLOGIC FINDINGS

The histologic features of postsecretory mammary involution have been described in considerable detail, and their description will not be repeated here.[3] No mastitis occurred in the 24 mice (including 10 mice treated with prolactin) whose young were removed at parturition or in the 14 mice whose litters were weaned at the end of the usual period of lactation. In all of the mice of these three groups the hematogenous and stromal reactions occurring during involution of the parenchyma were exceedingly mild. Macrophages, lymphocytes, plasma cells and other mononuclear cells were characteristic. Plasma cells increased in number during the active phases of involution. Heterophilic leukocytes were rare. The term "inflammation" is definitely not applicable to the reaction. Stromal responses and phagocytosis occurring during involution of the mammary parenchyma have been discussed elsewhere.[8]

The occurrence of mastitis was limited to mice whose young were removed during the height of secretory activity. That is, on the tenth day post partum, when lactation is at its peak. Inflammatory lesions were observed in 11 of the 76 mice so treated.

On the basis of certain histopathologic characteristics of the disease it is possible to classify the lesions roughly into two morphologic types. A diffuse type of mastitis, without obvious abscesses, occurred in 7 animals (including 2 testosterone-treated ones) which died or were killed one to five days after removal of the young. In 4 of these mice the lesions were present throughout all mammary glands, and in the remaining 3 mice, in one or two glands. The mastitis was lethal in 2 mice, and another animal was moribund when killed. In these 3 mice all ten glands were involved by the diffuse inflammatory process, and careful examination of all viscera revealed no evidence of disease other than mastitis. The mammary glands showed (fig. 1): (*a*) Secretory congestion of the duct system. The secretion had become very eosinophilic and hyaline in appearance. Milk stained by the methods used here is usually basophilic, vacuolar and granular in appearance. There were frequent intraluminal collections of heterophilic leukocytes. (*b*) Necrosis of alveolar and ductal epithelium, despite which the duct system had retained morphologically its mural continuity, and there was no evidence of secretion having escaped into the stroma. (*c*) Presence of an abundant interstitial and periductal exudate containing fibrin, many heterophils, lymphocytes and other mononuclear cells. In the case of earliest appearing mastitis (twenty-four hours after removal of the young) a diagnosis of acute mastitis may have been slightly premature. However, two glands of one mouse were so radically different from eighteen other glands chronologically representing the same stage of regression that some sort of differentiation was essential (fig. 3). In these two glands the duct system was excessively engorged with secretion. Further, the periductal and intraluminal leukocytosis (heterophils) was as extensive as that observed in any other animal of the series. There was generalized stromal edema. The duct system was intact.

In 4 mice (including 2 estrogen-treated ones) there were multiple nodular abscesses and large areas of new granulation tissue in some of the mammary glands. From such a mastitic gland the subsequently described Pasteurella was isolated. The abscess type of mastitis was observed in mice killed on the fifth and sixth days after removal of the young, and the disease was present in not more than two glands of a single animal (fig. 2). One observation weakens the validity of a division of the lesions into two types on the basis of the presence or the



Figures 1 to 4

(See legends on opposite page)

absence of abscesses and considerable areas of granulation. In glands which contained abscesses there were areas of congestion (ductal), parenchymal necrosis, interstitial and intraluminal leukocytosis, and stromal edema which were identical with the generalized inflammation here designated as diffuse mastitis. What has been described here as two morphologic types of mastitis may properly represent different stages in the same inflammatory process. Supporting the dual classification is the observation that the diffuse type consistently involved a majority of the glands in a given mouse, while the so-termed abscess type was limited to not more than two glands in a single mouse. However, the low incidence of the disease does not logically allow such deductions to be made from the data.

In noninflamed glands the stroma and the parenchyma were free from the changes just described except for a moderate degree of intraductal congestion and engorgement resulting from continued secretion during the earlier phases of postsecretory involution. Such stasis had usually terminated by the fifth day after the young had been removed during full lactation. In the normal sequence of events the significant features were cessation of secretion and progressive increase of the areolar stroma, which rapidly replaced the regressing parenchyma. Heterophils might or might not be present within the lumens of congested ducts. Periductal accumulations of leukocytes other than lymphocytes were most infrequent. Edema and exudation were absent, and the cellular elements characteristic of nonmastitic involution were lymphocytes, plasma cells, other mononuclear elements and obvious macrophages. In the normal glands there was at all comparable intervals following removal of the young much less congestion of the duct system than in the mastitic ones.

Thus far the descriptions have been limited to definite mastitis and to the usual ("normal") sequence of events in the postsecretory involution of the mammary parenchyma. Now to be considered are 6 instances in which there were definite alterations of the usual processes of mammary regression; yet designation of the condition as mastitis on the basis of the available stages of the processes is untenable in relation to the prior use of the term in this report. In 1 case the exceptional morphologic deviations were observed in the mammary parenchyma, in 4 the alterations were in the mammary lymph nodes, and in the remaining case both the mammary gland and the related lymph node were atypical.

In the first case a single mammary gland from a mouse killed four days after removal of the young showed great inequality in the extent or degree of parenchymal involution. In a greater part of the gland the amount of regression was usual for the chronologic interval of involution, while in some portions there was pronounced intraductal congestion with retention of secretion, intraluminal collections of heterophils, and stromal edema. In still another area of the gland there.

EXPLANATION OF FIGURES 1 TO 4

Fig. 1.—Typical mastitis occurring five days after a mouse was separated from her litter. Note the intraglandular congestion with retention of secretion, diffuse inflammation and parenchymal necrosis; × 100.

Fig. 2.—Mastitic gland, also on fifth day. The large ducts are engorged with secretion and contain many heterophilic leukocytes. There are many nodular abscesses; × 50.

Fig. 3.—Early stage of mastitis occurring after twenty-four hours of involution. The ducts and alveoli are filled with secretion and contain many heterophilic leukocytes; × 100.

Fig. 4.—Mastitis produced by inoculating the nipple area of a mammary gland with a culture of a Pasteurella isolated from a spontaneous case of mastitis; × 100.

were several large foreign body granulomas which seemed to have resulted from rupture of large ducts. Such areas contained heterophils, macrophages, many foamy epithelioid cells, and eosinophilic debris suggestive of residual secretion. There were necrosis and fibrosis of the fatty stroma. The related lymph node was not unusual.

In mice lymph nodes are located actually within or immediately adjacent to mammary glands. During lactation and postsecretory involution, these lymph nodes enlarge, and sinuses are dilated and contain many macrophages. In the cortex and the medulla there is an increase of hetrophils, macrophages and plasma cells. Plasma cells increase greatly in number, particularly in the hilar perivascular areas. Edema and hyperemia are fairly generalized. In the previously described mastitic glands the appropriate lymph nodes showed no significant additional and concomitant reactions which might be specifically correlated with the acute and probably early phases of the intraglandular inflammation. However, in 3 mice the lymph nodes related to only one mammary gland, and in another mouse the lymph nodes of two mammary glands (thoracic and lumbar) showed definite abnormality. In the first three nodes (from mice killed five, eight and ten days after being separated from their young) there were abscesses. In the two other lymph nodes (both from a mouse killed twenty days after removal of the young) there was a great increase in heterophils, a decrease in free lymphoid cells and almost an obliteration of the usual nodules of lymphoid cells. The five mammary glands directly drained by these nodes were definitely not mastitic at the time, nor was there any clear evidence of fibrosis which might indicate preceding severe inflammation. Yet the condition of the lymph nodes did suggest that there had been some aberration during the single preceding gestation, ten days of lactation or period of involution. In the sixth case there were numerous giant cells and accumulations of heterophils in a single mammary lymph node of a mouse killed six days after being separated from her young. The related mammary gland showed areas of fibrosis which still contained mononuclear cells and remnants of parenchyma, but there was no active inflammation Most of this particular gland appeared normal.

BACTERIOLOGIC FINDINGS

The original isolation of an organism identified as a Pasteurella was made from a single mastitic gland of the abscess type obtained from a mouse killed on the fifth day after removal of the young. The mastitis was limited to the one third of the gland most proximal to the nipple. A portion of the gland was streaked on a veal infusion–agar slant. Similar cultures of other mammary glands, spleen and lymph nodes did not show bacteria. Various morphologic and biochemical tests were applied to subcultures of the aforementioned organism.

Morphologic Observations.—Gram stains showed strongly gram-negative short rods with evident bipolar staining. Both solid and liquid mediums produced these typical forms at twenty-four hours, but at five to seven days coccoid and coccobacillary forms predominated. Definite pleomorphism could be noted in cultures of any age. Hanging drops were prepared from young cultures (four to eight hours). The organisms were nonmotile. Capsule stains (Welch and Maneval) proved negative in twenty-four hour cultures. Spore stains were negative on six day cultures. The organisms were neither alcohol nor acid fast.

Experimental Observations.—The 4 mice which had received injections of a culture of the organism into the nipple area of the right lumbar mammary gland were killed seven days later (also the seventh day after removal of the young). Such glands showed typical nodular abscesses throughout the entire inoculated gland. The

lymph nodes related to the glands were greatly enlarged. In addition to the abscesses there were foci of granulation tissue, many collections of heterophilic leukocytes and areas of parenchymal necrosis (fig. 4). Mastitis was limited to the inoculated glands, and the animals appeared in good health. The general histopathologic appearance was comparable to that observed in 4 mice in which mastitis developed spontaneously. There were areas of stromal inflammation and parenchymal necrosis similar to those seen in all of the cases of spontaneous mastitis studied here. Cultures of mammary glands, lymph nodes and spleen showed the micro-organism to be limited to inoculated mammary glands and adjacent lymph nodes. Mammary glands into which sterile broth had been injected showed no inflammatory reaction seven days later.

COMMENT

The study demonstrates that in the mouse an uncomplicated (by disease) rapid parenchymal involution usually attends the cessation of normal drainage of the mammary gland when the suckled litters are removed during full lactation. In by far a minority of the mice (11 of 76 mice) lactation continued and a condition of massive intraductal congestion, due to retained secretion, and subsequent severe inflammation resulted. This reaction was apparently not evoked simply by the great amount of secretion retained within the duct system or by any which escaped into the interstitium. The latter occurrence was not observed in these mice. The inflammation was much more extensive and severe than that which followed ligation of galactophores with ensuing ectasia and rupture of ducts, extravasation of secretion and resulting cellulitis. Of sixteen suckled but ligated (galactophores) mammary glands of 18 mice, only four showed inflammation, and in such "mastitic" glands galactoceles developed and an inflammatory response was elicited by the secretion released into the stroma.[4] The stromal reactions in the ligated glands which showed inflammation resembled those described here as foreign body granuloma. The response of hyperplastic mammary glands of non-nursing mice induced by injection of prolactin shows that undrained mammary glands can tolerate extensive intraductal engorgement and congestion due to retention of secretion without the occurrence of inflammation.[5]

Although it was indicated that an excessive amount of secretion retained within the duct system was an important contributing factor in the processes which resulted in acute inflammation, it seems likely that another etiologic agent was operating in those relatively few cases in which mastitis occurred. The abscesses, edema, exudation, extensive parenchymal and stromal leukocytosis, and parenchymal necrosis suggest the presence of an infectious organism. Unfortunately, in most instances, mastitis was not suspected until autopsy, and the lack of

4. Williams, W. L.: Yale J. Biol. & Med. **14**:201, 1941.

5. Hooker, C. W., and Williams, W. L.: Endocrinology **28**:42, 1941. Williams, W. L.: Anat. Rec. **93**:171, 1945.

aseptic procedures did not allow bacteriologic studies. In 1 case of mastitis a Pasteurella was isolated, which later produced mastitic lesions when inoculated in mammary glands of mice. It has been reported that Pasteurella organisms are a cause of mastitis in cattle and sheep.[6]

In the presence of normal drainage of the duct system a state of full lactation is usually attained in the mouse on the fourth day post partum.[7] Therefore, when the litter is removed at parturition, the parenchymal regression of the mammary gland is rapid, and retained secretion is no problem. In mice whose young were removed on the fourth day post partum, no severe intraductal stasis and definitely no inflammation was observed.[8] If lactation continues, with the original litter being nursed, involutional changes occur during the terminal three to four days of the usual twenty-one day period.[7] Therefore, subsequent to weaning of the young twenty-one days post partum, cessation of secretion and rapid parenchymal involution ensue. It is apparently only when normal drainage ceases during the height of full secretory activity that engorgement of the duct system becomes a problem for an interval of significant duration. Usually, natural mechanisms seemed able to cope with the situation. As mentioned previously, bacterial infection was definitely proved in only the one case, while in all cases of mastitis the duct system was massively engorged with retained secretion. It is important to remember that such ductal congestion and stasis are usual during the first three to four days subsequent to removal of the young when this occurs during the height of secretory activity. Yet, definitely only a minority of the animals subjected to such a situation showed any evidence of mastitis.

Mastitis was observed in only 11 of 76 mice which were separated from their litters on the tenth day post partum. The total group included spayed mice, hypophysectomized mice and mice treated with glandular products. If intraductal congestion is of significance in mastitis, the hypophysectomized mice should not be included in the determination of incidence of the disease. Removal of the hypophysis at the time of segregation of the litters caused immediate cessation of secretion and great acceleration of the regression of the mammary parenchyma.[8] The opposite type of experimental procedure—injection of the lactogenic substance, prolactin—retarded parenchymal involution under similar circumstances.[5] Injections of estrogen, progesterone and testosterone propionate, as well as ovariectomy, were without effect on postsecretory mammary involution.[8] Therefore, that mastitis did or did not occur in ovariectomized mice or in mice treated with the aforementioned substances is most probably of no absolute or relative significance if the

6. Packer, R. A., and Merchant, I. A.: North Am. Vet. **27**:496, 1946. Marsh, H.: J. Am. Vet. M. A. **34**:376, 1932.

7. (*a*) Cole, H. A.: Proc. Roy. Soc., London, s.B. **114**:136, 1933. (*b*) Williams.[a]

8. Hooker, C. W., and Williams, W. L.: Yale J. Biol. & Med. **12**:559, 1940.

fact that these procedures had no effect on the processes of involution in normal mice is a valid consideration. Also, the number of mice in the group operated on and the groups treated with glandular products, taken separately or collectively, is too small for a positive correlation.

The lesions definitely demonstrated acute inflammation. In 3 mice all glands were involved, and the mastitic disease was lethal. In 8 mice one or two glands were diseased. The question arises as to what would have been the course of the disease in these animals if they had not been killed at the time. The data allow no answer. Except during pregnancy, lactation and a short interval after cessation of lactation the mammary parenchyma of the mouse consists almost entirely of the major duct system. A fatty areolar stroma replaces the lobule-alveolar pattern of the hyperplastic gland. Areas of fibrosis which might indicate a scar were not observed except in 1 case. Likewise there were no unusual accumulations of leukocytes. In 5 mice killed five to twenty days after removal of the young the adjacent lymph nodes showed abscesses and other indications of recent inflammation, although the glandular tissue itself did not display mastitis. The related lymph nodes show such striking changes during "normal" involution that no specific intranodal alterations could be correlated with the definite mastitis seen in 11 mice. From an etiologic consideration at least three factors acting alone or collectively seem to be of significance. They are: (*a*) the reaction of stroma and parenchyma induced by the massive congestion and stasis which resulted in the residual but involuting duct and alveolar system when secretion continued in the absence of drainage; (*b*) in some instances an escape of retained secretion into the stroma; (*c*) infection.

Morphologically, the lesions described here simulate some forms of mastitis in man and in dairy animals. How do they compare with inflammatory mammary lesions previously described in mice? They are not similar to the chronic, rather low grade inflammatory conditions common to mice on extended treatment with estrogens. Such lesions are considered in the reviews of Gardner and of Taylor and associates.[1] Several studies have not discussed acute inflammation in relation to postsecretory involution of the mammary gland of the mouse.[9] The same is true for studies of the guinea pig, the rat, the cat and the dog.[10]

9. (*a*) Turner, C. W.: The Comparative Anatomy of the Mammary Gland, Columbia, Mo., University Cooperative Store, 1939, p. 234. (*b*) Turner, C. W., and Gomez, E. T.: Research Bulletin 182, Missouri Agricultural Experiment Station, 1939. Cole.[7a]

10. Kuramitsu, C., and Loeb, L.: Am. J. Physiol. **56**:40, 1921. Turner, C. W., and Gomez, E. T.: Research Bulletin 194, Missouri Agricultural Experiment Station, 1933. Maeder, L. M.: Am. J. Anat. **31**:1, 1922. Turner, C. W., and Schultze, A. B.: Research Bulletin 157, Missouri Agricultural Experiment Station, 1931. Turner, C. W., and DeMoss, W. R.: Research Bulletin 207, ibid., 1934. Turner and Gomez.[9b]

Mastitis was not observed in mice in which some degree of lactation without drainage was maintained by experimental methods.[8] Lesions of a possible chronic cystic type have been described in certain high tumor strains of mice.[11] An undescribed type of acute mastitis has been reported in Dba mice.[12] Such reports as those just cited, as well as the data presented here, demonstrate that acute mastitis is infrequent in mice. Even under the fairly atypical conditions described here the occurrence of acute inflammatory lesions of the mammary glands of the mouse is not common.

SUMMARY

Mastitis occurred in 11 of 76 mice during postsecretory mammary involution which had been produced by separating the mothers from their litters at approximately the midpoint of the usual period of lactation. Extensive inflammatory lesions were observed in 1 to 10 (all) of the mammary glands of individual mothers killed one to six days after being separated from their litters. In 5 additional mice, there was no active mastitis at the time at which they were killed, but the adjacent lymph nodes showed some evidence of recent inflammation. In all instances mastitis was definitely associated with extensive intraductal stasis and congestion which resulted as milk formation continued in the absence of normal drainage.

Cultures of mammary glands which showed no histologic evidence of mastitis revealed no micro-organisms. A Pasteurella was isolated from a case of mastitis, and a subsequent culture inoculated into the nipple area produced mastitis throughout that gland.

Ovariectomy and injections of estrone, progesterone and testosterone propionate did not alter the rate or the pattern of the involution of the parenchyma. Mastitis occurred in 4 of 12 mice which had been treated by injection of estrone or testosterone propionate. Hypophysectomy accelerated involution of the parenchyma, and injections of prolactin retarded it.

11. Gibson, L. M.: J. Cancer Research **14**:570, 1930.
12. Fekete, E.: Am. J. Path. **14**:557, 1938.

ROLE PLAYED BY THE SALIVARY GLANDS IN THE "ALARM REACTION"

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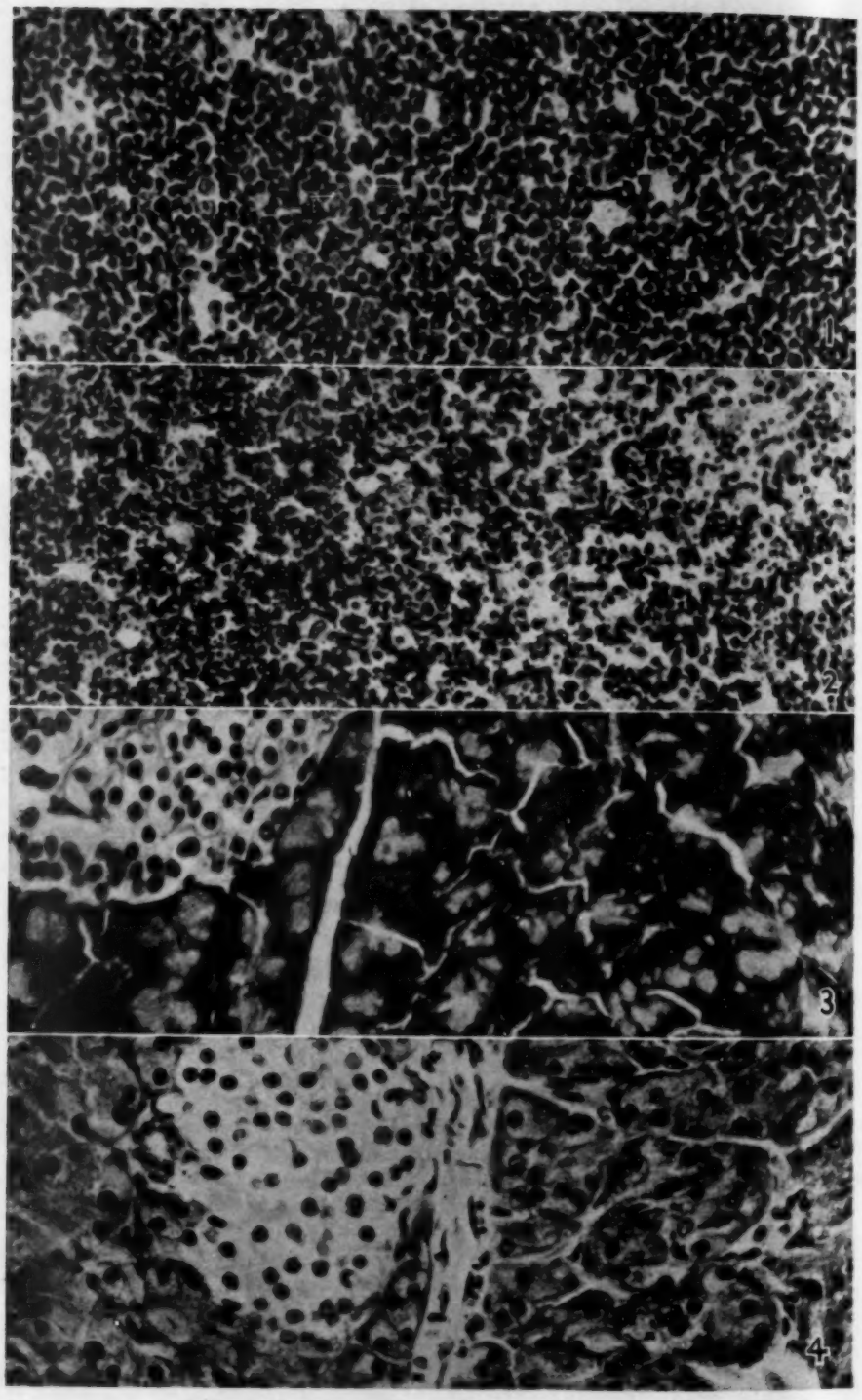
THE alarm reaction of Selye may be defined as an acute morbid response occurring in the organism when the latter is in the process of adapting to stresses of the environment. There is first a shock phase in which adrenotropic hormone is released from the anterior lobe of the pituitary gland. This causes the adrenal gland to release cortical hormones (Selye [1]; Long [2]). Resulting from this endocrine sequence there is a second or countershock phase during which general tissue changes are most conspicuous.

According to Selye,[1] the organs particularly affected by the alarm reaction are the thymus, the spleen, the lymph nodes, the gastrointestinal tract, the pancreas and the liver. The thymus, the spleen, the lymph nodes and the gastrointestinal tract reveal shedding of cytoplasm and necrosis of lymphocytes and plasma cells. The pancreas and the liver show loss of basophil granules and in some cases necrosis as well.

All these organs are known to contain large concentrations of nucleic acids, particularly ribose nucleic acid (Jorpes [3]; Davidson and Waymouth [4]; Schneider and Klug [5]). If these acids are a factor in the alarm reaction, other tissues rich in them should be affected in the same way. Consequently, we investigated the salivary glands, which have a high concentration of ribose nucleic acid (Jorpes [3]; Caspersson, Landström-Hydén and Aquilonius [6]).

From the Philadelphia General Hospital and the Wyeth Institute of Applied Biochemistry.

1. Selye, H.: J. Clin. Endocrinol. **6**:117, 1946.
2. Long, C. N. H.: Read at the Thirty-First Annual Meeting, Joint Session of the Federation of American Societies for Experimental Biology, Chicago 1947.
3. Jorpes, E.: Acta med. Scandinav. **68**:253, 1928.
4. Davidson, J. N., and Waymouth, C.: Nature, London **152**:47, 1943; Biochem. J. **38**:39, 1944.
5. Schneider, W. C., and Klug, H. L.: Cancer Research **6**:691, 1946.
6. Caspersson, T.; Landström-Hydén, H., and Aquilonius, L.: Chromosoma **2**:111, 1941.



Figures 1 to 4

(See legends on opposite page)

EXPERIMENTS

The pertinent observations were made on white rats that had been given large doses of colchicine by injection. This drug, according to Leblond and Segal,[7] is the most alarming stimulus yet described. Other animals were dosed with different chemical stimuli and their organs examined to determine whether the alarm reaction would be of value in studying the comparative toxicity of drugs. These studies also included animals that had died of pneumonia and other acute diseases.

1. The rats treated with subcutaneous injections of colchicine were 46 or 48 days old. Six of them received 5 mg. of drug per kilogram of body weight; 8, 7 mg., and 17, 10 mg. per kilogram. Death occurred in 10 rats eighteen to twenty-eight hours after receiving the higher doses. The remaining animals were killed at intervals of from two to twenty-eight hours.

The rats presented most of the histologic changes described by Selye[1] as characteristic of the alarm reaction. The adrenal glands showed loss of lipoid substance, hemorrhagic degeneration and cortical necrosis. There was almost complete pyknonecrosis of the lymphocytes and the plasma cells of the thymus (figs. 1 and 2), the lymph nodes, the spleen and the gastrointestinal tract. There was marked loss of zymogen granules of the pancreas, occasionally with focal necrosis (figs. 3, 4 and 5). There were no significant changes in the kidneys, the liver and the thyroid gland. Most of these effects were apparent two hours after injection, became more marked after six hours and were severe after eighteen hours. The pyknonecrosis of the lymphocytes and the plasma cells of the lymphoid organs was followed by phagocytosis of the debris and subsequent proliferation of the macrophages, particularly in the secondary nodules, whose lymphoblasts were replaced by these cells.

The salivary glands of these rats were severely affected by the alarm reaction as we had anticipated on the basis of the nucleoprotein hypothesis. The morphologic changes closely resembled those we had seen in the pancreas. There was marked loss of zymogen granules (figs. 6, 7, 8, 10 and 11), and in advanced cases there were foci of necrosis (fig. 11). These changes occurred in all the salivary glands that were examined.

2. Rats, rabbits and dogs were treated with other alarming stimuli, which included aminopyrine (1.0 per cent), diacetylthiourea (0.1 per cent), 2-aminothiazole (250 to 400 mg. per kilogram, dogs), selenium dioxide (0.005 per cent), sodium selenite (0.005 per cent), bis-(4-acetaminophenyl) selenium dihydroxide (0.1 per cent), diaminodiphenylsulfone (0.25 per cent), diaminobenzophenone (0.125 per cent), digitalis (1 unit per day, rabbits). Most drugs were given for a week or two; the

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EXPLANATION OF FIGURES 1 TO 4

Fig. 1 (normal rat).—Cortex of well developed thymus. Hematoxylin-eosin; × 460.

Fig. 2 (rat killed twenty-six hours after subcutaneous injection of 7 mg. of colchicine per kilogram).—Advanced pyknonecrosis of cortex of thymus with macrophages phagocytosing debris. Hematoxylin-eosin; × 460.

Fig. 3 (normal rat).—Pancreas showing abundant zymogen granules (dark material in photo). Hematoxylin-eosin; × 460.

Fig. 4 (rat killed twenty-two hours after subcutaneous injection of 10 mg. of colchicine per kilogram),—Loss of zymogen granules and atrophy of excretory epithelium of pancreas. Hematoxylin-eosin; × 460.

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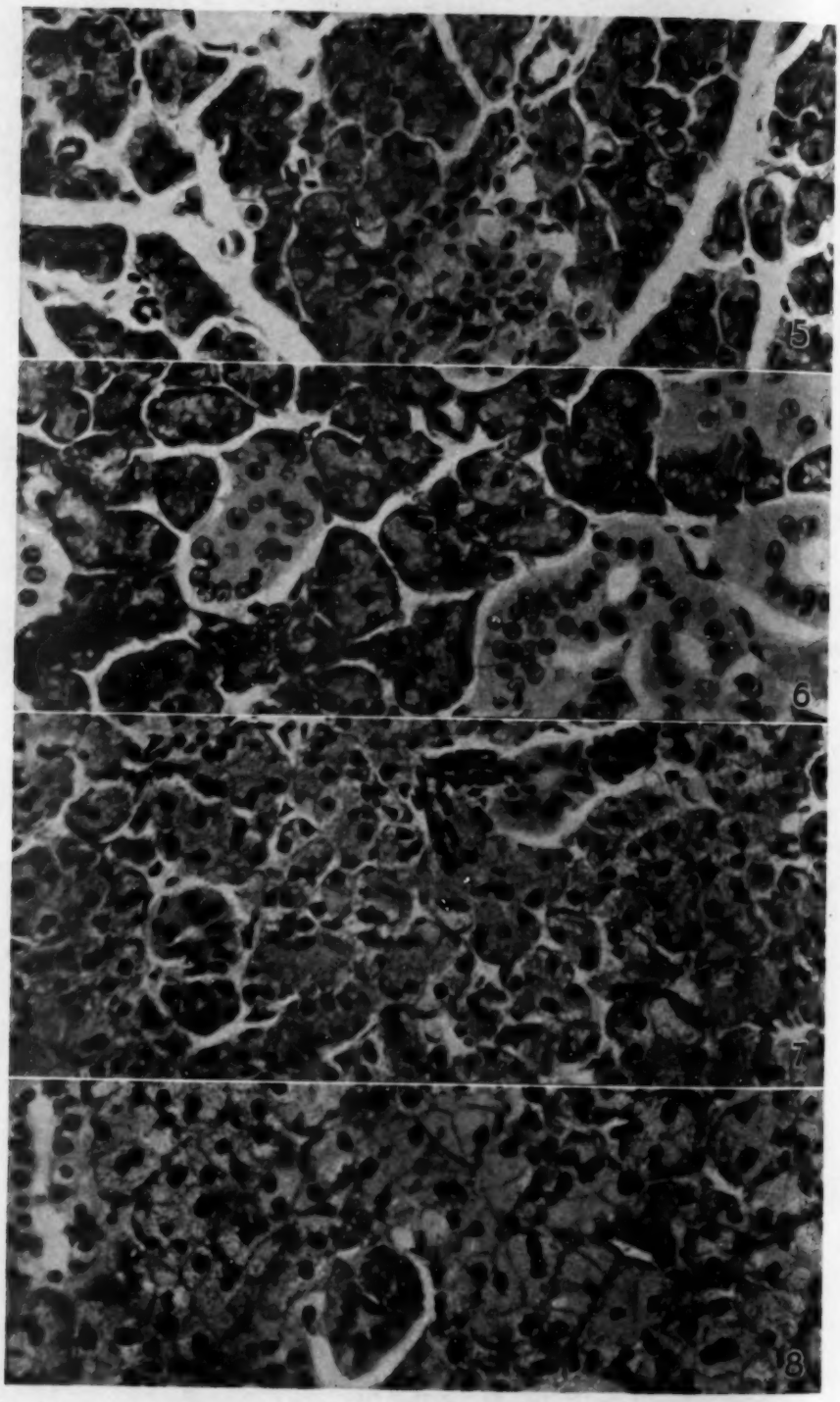
7. Leblond, C. P., and Segal, G.: Compt. rend. Soc. de biol. **128**:995, 1938.



Figures 5 to 8

(See legends on opposite page)

rest for several weeks or months. Some of these animals showed both alarm reaction and pneumonia at autopsy, but similar changes were seen in untreated animals that had died of pneumonia. This is interpreted as indicating that severe infection is an alarming stimulus.

In this series of animals, as in the group treated with colchicine, the lymphoid organs and the pancreas were most conspicuously affected. The lymphoid organs showed pyknonecrosis of lymphocytes and plasma cells and subsequent removal of the debris by proliferating macrophages, and the pancreas showed loss of zymogen granules and occasional foci of necrosis (fig. 9). The salivary glands showed essentially the same changes as those described in the foregoing section. There was marked loss of the basophil matter of the secreting epithelial cells, and in more severe cases there was also focal necrosis of these cells (fig. 12).

COMMENT

The results of the experiments seem to bear out the a priori thinking. It is demonstrated that organs rich in nucleic acids, particularly ribose nucleic acid, participate in the alarm reaction. Changes provoked by the alarm reaction in the salivary glands are described for the first time; the morphologic response of these glands closely resembles that observed in the pancreas. What further role the nucleic acids play in the alarm reaction was not investigated at this time, but it was postulated that they are important intermediaries of the effect exerted by the adrenal cortical hormones on lymphocytes, plasma cells, zymogen granules and similar basophil material.

These observations have practical significance as affording a possible explanation of the etiology of the "symptomatic" parotitis that develops after operations or during severe infectious diseases. It has long been known that this sialadenitis is not metastatic but is due to infection with micro-organisms, especially staphylococci, already present in the mouth (literature reviewed by Custer [8] and by Coughlin and Rutledge [9]). It is also known that postoperative parotitis occurs particularly after abdominal operations which are likely to cause shock, such as operations on the

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Explanation of Figures 5 to 8

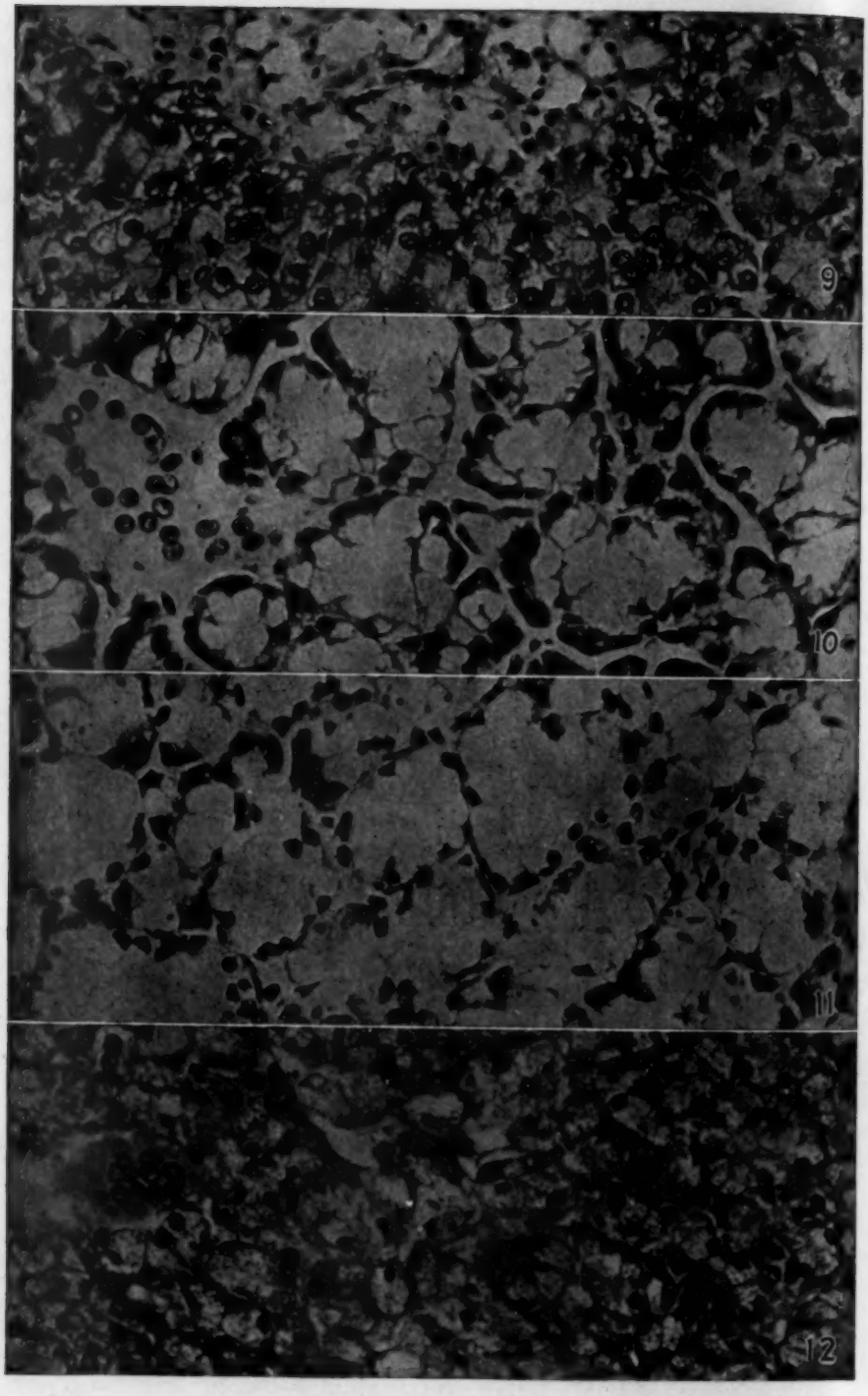
Fig. 5 (rat killed twenty-six hours after subcutaneous injection of 7 mg. of colchicine per kilogram).—Loss of zymogen granules and marked atrophy of excretory epithelium of pancreas. Hematoxylin-eosin; × 460.

Fig. 6 (normal rat).—Salivary gland showing considerable concentration of basophilic material, especially at base of secretory cells. Hematoxylin-eosin; × 460.

Fig. 7 (rat killed twenty-six hours after a subcutaneous injection of 7 mg. of colchicine per kilogram).—Salivary gland showing marked loss of basophilic material and atrophy of excretory epithelium. Hematoxylin-eosin; × 460.

Fig. 8 (rat killed twenty-two hours after subcutaneous injection of 10 mg. of colchicine per kilogram).—Salivary gland showing marked loss of basophilic material. Hematoxylin-eosin; × 460.

8. Custer, R. P.: Am. J. M. Sc. **182**:649, 1931.
9. Coughlin, W. T., and Rutledge, E.: Arch. Surg. **45**:361, 1942.



Figures 9 to 12

(See legends on opposite page)

colon (1 in 135 cases, Rankin and Palmer [10]; 1 in 125 cases, Crile and Manning [11]) or abdominoperineal resection of the rectum (1 in 20 cases, Crile and Manning [11]). The ease with which the infection occurs has been variously attributed to: lowering of general resistance; diminution of salivary flow due to dehydration following excessive vomiting or purging; reflex inhibition of salivation brought about by anesthesia or visceral manipulations; direct traumatizing of the glands by the anesthetist.

Diminution of salivary flow is obviously a factor in the causation of symptomatic parotitis, but it does not account for the gland's being infected by micro-organisms present in the mouth. Undoubtedly, sufficient lowering of local tissue resistance must also occur to render the gland susceptible to infection. It is likely that the changes described in this paper represent the initial injury, and it may be that the diminution of salivary flow is a sequel to them.

SUMMARY AND CONCLUSIONS

An alarm reaction was produced experimentally in rats, dogs and rabbits with large doses of colchicine, aminopyrine, selenium compounds and other drugs. It was found that the salivary glands participate in this reaction. As in the pancreas, there was marked loss of zymogen granules, and in severe cases there was also focal necrosis.

It is possible that the alarm reaction plays a role in the causation of parotitis following operation. It is not unlikely that at least in some cases this sialadenitis is merely another part phenomenon or sequel of this reaction.

EXPLANATION OF FIGURES 9 TO 12

Fig. 9 (rabbit which died spontaneously with aspiration pneumonia after having received 1 unit of digitalis per day for six weeks).—Pancreas showing loss of zymogen granules, atrophy and focal necrosis of excretory parenchyma. Hematoxylin-eosin; × 460.

Fig. 10 (normal rat).—Mucoid salivary gland showing considerable concentration of basophilic material especially at base of secretory cells. Hematoxylin-eosin; × 460.

Fig. 11 (rat killed twenty-two hours after subcutaneous injection of 10 mg. of colchicine per kilogram).—Loss of basophilic material and pyknonecrosis of mucoid salivary gland. Hematoxylin-eosin; × 460.

Fig. 12 (rabbit which died spontaneously with aspiration pneumonia after having received 1 unit of digitalis per day for six weeks).—Salivary gland showing loss of basophilic material and focal necrosis of excretory parenchyma. Hematoxylin-eosin; × 460.

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10. Palmer, B. M., and Rankin, F. W.: Ann. Surg. **92**:1007, 1930.
11. Crile, G., and Manning, W.: Am. J. Surg. **50**:664, 1940.

NORMAL VARIATION OF THE COSTOCHONDRAL JUNCTION

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AS ROUTINE autopsy specimens of bone and cartilage, the costochondral junctions are easily accessible to the pathologist. Those of children permit examination of a region of active endochondral bone growth as well as one of hemopoiesis.

In this paper an attempt will be made to show that specimens of growing bone of children often disclose nonspecific as well as specific changes which result from disease or nutritional deficiency and to demonstrate that normal variation in histologic structure has a close relation to the age of the child. I shall describe the costochondral junction in detail to facilitate differentiation between the variations in histologic structure to be found normally and the nonspecific and specific changes seen in various diseases. In the literature I have found no reports which discuss variations of the normal histologic pattern of growth.

Specimens of costochondral junctions, cut anteroposteriorly, have been taken routinely in this laboratory for many years; ribs obtained in over 500 autopsies have provided the material for this paper. Special attention has been paid to those of children under the age of 2 years. The material was divided into four groups: The first was selected to provide substantial numbers of ribs from certain age groups as listed, without regard to general or local pathologic processes present, provided the disease was of relatively short duration and disturbance of bone growth was not anticipated. The second group was selected to illustrate different types of growth and of pathologic disturbance occurring in the area. The ribs of a third group of 10 infants from 3 days to 2 years of age had their arterial systems injected via the internal mammary artery with colored latex solution in order that the fine arterial supply of the costochondral junction might be studied. The last group consisted of the ribs of 10 infants with coarctation of the aorta, which were studied for reasons given later.

ANATOMIC INTRODUCTION

A short account of the anatomy of the ribs will be presented first. The following description is based on material found in Lexer,[1]

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1. Lexer, E.: Untersuchungen über Knochen-arterien, Berlin, A. Hirschwald, 1904.

von Langer,[2] Schmidt [3] and Park,[4] supplemented by the present study of the injected arterial supply of ribs. The body of the rib has one center of ossification which is well developed at birth. A variable and progressively decreasing proportion of the anterior part of the thorax consists of costal cartilage which undergoes endochondral ossification at the costochondral junction. This process provides the rib with its principal increment in length.

The arteries supplying the arch of each rib are the aortic and anterior intercostal arteries, which arise segmentally from the aorta and the internal mammary artery, respectively. The lower five ribs are supplied anteriorly by branches from the musculophrenic branch of the internal mammary artery, while the supreme intercostal artery (from the costocervical trunk, a branch of the subclavian artery) supplies the first two ribs posteriorly; thus each rib and its cartilage have an anterior and a posterior blood supply, with the anastomosis occurring at the osteochondral junction. This anastomosis has been the subject of some study because of the prevalent opinion (Harris [5]) that anastomosis does not occur across epiphysial cartilage. The costal cartilage of the rib, because of its endochondral conversion into bone, may be considered an epiphysial cartilage, even though it contains no separate center of ossification. Therefore, the arteries of the region are worthy of description. The perichondrial arteries (from the anterior intercostal artery) course nearly circularly around the cartilage. They arise, according to Schmidt, at regular intervals and give off occasional branches which penetrate the cartilage.[6] I have observed regularity in the branching of the anterior intercostal artery only occasionally, and I have been impressed with the great variation in the number of perichondrial branches and also in the number of twigs penetrating into the cartilage. A perichondrial artery of moderately large size is usually found at the osteochondral junction, and a vessel penetrating into cartilage is also rather constantly present at the costal (distal) extremity of the cartilage. The vessel or vessels penetrating the cartilage do so through

2. von Langer: Denkschr. d. k. Akad. d. Wissensch. **31**:1, 1872; **36**:1, 1876.

3. Schmidt, M. B.: Rachitis und Osteomalacie, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1935, vol. 9.

4. Park, E. A.; Jackson, D.; Goodwin, T. C., and Kajdi, L.: J. Pediat. **3**:265, 1933.

5. Harris, H. A.: J. Anat. **54**:3, 1929.

6. The only other reference to this detail of the circulation available in the literature is a diagram published by M. Ribert (Les arteres osteo-articularies, Algiers, Imprimerie moderne, p. 52, 1926), which illustrates the variability from rib to rib. Ribet makes no comment concerning this variability, nor does he imply that the figure is more than a diagrammatic representation.

the canals of the cartilage. These also contain one or more commonly, two veins, as well as a small amount of loose connective tissue, in which a rather sparse capillary network ramifies. The canals contain vessels that in general appear large in relation to their bed. This is especially true of the distal canal, which is the largest of all and contains the largest vessel. The vessels of the cartilage canals, along with the perichondrial vessels, supply the cartilage with its nutrition. The formation of cartilage canals occurs by invagination of the connective tissue and vessels of the perichondrium. According to von Langer, these cartilage canals appear at about the third month of fetal life, and there is continuous formation of new canals even after birth until the age of 1 year. The significance of the perichondrial origin of the loose embryonic-looking tissue within the canal is apparent when one considers the fate of the connective tissue of the canal as osteogenesis progressively obliterates the canal. No trace of this embryonic tissue can be found in the marrow cavity of the ribs. The disappearance of such quantities of connective tissue is difficult to explain unless one assumes that these cells retain their original potentialities and merge with the marrow tissue, which has a similar origin and potentialities. In this connection it may be mentioned that the osteoblasts of the bone marrow have their origin from the original perichondrium at the stage when the original cartilage anlage is invaded by vascular mesenchymal tissue.

The enlargement of the distal canal occurs by continuous growing of embryonic tissue from the perichondrium. The rather constant finding of a large distal canal may be explained by the continual vascular penetration of the cartilage, since often no other penetrating canals are seen. This canal is uniformly placed in relation to the proliferative zone of the cartilage cells. Often vessels are seen which seem to penetrate only small distances into the cartilage, but since no studies of serial sections were made, verification of continual penetration and histologic study of the penetration were not possible.

Frequently one sees a communicating bridge of embryonic tissue containing a small vessel which crosses the proliferative band of cartilage undergoing endochondral ossification and connects the marrow cavity with the last cartilage canal. This vascular connection between cartilage canal and marrow cavity seemingly contradicts Harris' statement [5] that no such vessels anastomose across areas of epiphysial growth, but the uniformly small caliber of the anastomotic vessel and, indeed, its inconstant occurrence argue against any essential participation in the growth mechanism. The blood vessel present in or near the zone of endochondral ossification evokes local changes in the chemistry of the connective tissue matrix, for often one may discern in the accompanying embryonic connective tissue an eosinophilic matrix with lacunas and cells resembling those

in the bone. In similar fashion this phenomenon of tissue resembling bone abutting against cartilage often may be seen at the distal border of the cartilage peripherally and at the point where the canal penetrates the cartilage.

At this point a paragraph may be devoted to the fate of the vessels in the canals after the area has been incorporated into the marrow. No obliterative endarteritis is seen in the walls of the arteries of the cartilage canals. This mitigates against the hypothesis of closure of an unneeded vessel analogous to the closure of the ductus arteriosus and umbilical arteries. However, one finds no traces of arteries of this size in the marrow. Frequently there is seen at the distal portion of the marrow one or two thin-walled veins running parallel to the osteochondral line. These may be the remains of the canal veins. Schmidt stated:

> . . . When the bone progresses with its marrow into the cartilage during growth, it finds a vascular network already present, which is continuous with its own. The original cartilage vessels are taken over as marrow vessels—the longitudinal vessels of the bone marrow do not elongate during growth by sprouting toward the epiphysis but by amalgamating with the cartilage canal arteries. The capillaries which are found in the youngest marrow space of the growing bone are not related to the cartilage vessels but are new branches of the capillary net of the marrow.

I could not confirm the amalgamation of these arteries, but neither could I discover their ultimate disposition.

The periosteal circulation provides the surface of the rib with many small vessels, the arrangement of which is not distinctive. The degree to which these anastomose with the perichondrial circulation and particularly with the arterial loops is minimal even though in the surrounding soft tissues the anastomosis is extensive.

The circulation of the marrow arises from the nutrient artery, with subsidiary branches entering through Volkmann's canals. The nutrient artery enters the rib at the level of the tubercle, and immediately divides into a large anterior and a smaller posterior branch. The anterior branch courses on, giving off small twigs to the marrow, which anastomose with the branches perforating from the periosteum. Near the osteochondral line many arcades of thin-walled vessels occupy the space between trabeculae of the cartilage matrix. These are the ultimate branches of the nutrient artery. One or more of these arcades anastomose with the chondral circulation as described. Frequently, near the osteochondral line, one or two broad veins running parallel to the osteochondral line are seen. These probably are the remnants of the veins of the cartilage canals. Their fate is unknown.

The microscopic appearance of the costochondral junctions is similar to that of any epiphysial cartilage undergoing endochondral ossification. Resting and proliferating zones of the cartilage are easily recognized just

as in any epiphysial cartilage. The endochondral ossification zone begins where the resting cartilage is transformed into proliferating cartilage, in the neighborhood of the last cartilage canal. By "resting cartilage" is meant the cartilage which, though growing slowly by division and multiplication of the chondrocytes and production of matrix, is not increasing its volume as rapidly as that portion of cartilage undergoing the sequences preparatory to ossification (cytomorphosis).[7] The proliferating cartilage strip has been variously divided by different workers into two or more zones, every one recognizing a gradual maturation of cells until ultimately the columns of mature cells are entered by marrow vessels. It is not intended to outline here the processes of ossification. However, several details must be mentioned to supplement the usual descriptions. Usually a layer of cartilage about 10 to 15 cells in thickness is described as intervening between the resting zone and the zone of mature cartilage cells. In this layer the chondrocytes multiply rapidly, group themselves into four cell aggregates and then aline themselves in rows, all the while enlarging, so that the matrix present becomes compressed into longitudinal columns. At the distal ends of these columns lie the mature cells, which usually number 4 per column. Thin septums of matrix separate the cells, but rather thick pillars of matrix are present between cell columns. This zone is also characterized by calcium deposited in the cartilage matrix and alkaline phosphatase in the cells as shown by the Gömöri stain. The deposited calcium is usually found only in the distal half of the zone, and there, in the matrix only. The phosphatase is found only in the cells, and there, mostly in the nuclei. The transverse septums as well as the longitudinal pillars of matrix contain deposits of calcium as shown by Bloom and Bloom.[8] At the distal end of the cartilage cell column is the complex of penetrating marrow vessels separated by trabeculae of cartilage matrix, on the sides of which bone is being deposited. The simultaneous assurance of structural strength and easy remodeling is accomplished in this area by a thin periosteal bony layer and thin bands of bone which reach from the calcified trabeculae to the bony cortex. The thicker layer of cortical bone of the rib is subpleural, and the larger buttresses are also internal. Parenthetically it may be remarked that beading, when present, is usually more marked internally than externally. Normally, slight beading internally may be seen. This is an expression of the greater stress at the internal portion of the rib during respiratory movement and consequent increased production of bone.

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7. "Cytomorphosis" is the term which designates the transformation of the cartilage cells preparatory to ossification, i. e., their rapid multiplication and columnar arrangement, with maturation and death of the chondrocyte occurring as the vascular marrow enters the capsule of the cell.

8. Bloom, W., and Bloom, M. A.. Anat. Rec. **78**:333 and 497, 1940.

NORMAL VARIATION

Interest in the normal variation of histologic features was occasioned by the difficulty that was experienced in this laboratory in interpreting the histologic aspect of the costochondral junction as a recorder of vitamin deficiency or other disturbance of growth during the first two years of life. It was evident that the normal would have to be described, and at once difficulties arose. The statistical approach was decided on, and specimens were collected to provide significant numbers in each of the age groups listed. Sudden death without some antecedent disease is especially rare in these age groups, and specimens had to be selected in cases in which minimal duration of disease processes was evident (usually less than one week). Dodds and Cameron [9] stated that experimental rachitic changes can be seen twenty-four hours after an animal is started on a rachitogenic diet and that progressive changes of the thickness of the mature cell layer of cartilage occur after one week in rats. Therefore, even short periods of dietary deficiency can produce significant changes, but care must be taken in correlating experimental and clinical data in view of the well known differences of species in regard to vitamin storage and synthesis. In the cases studied in this laboratory it was a rarity to find adequate diets up to the time of death. The injection of parenteral fluids, the frequent occurrence of diarrhea or vomiting and the infrequent use of injectable vitamins during maintenance by parenteral fluid render the statistics to be presented as "normal variations" extremely questionable if the term is to be taken literally. I use the term, therefore, to include the usually short period of illness and the consequent dietary abnormality, and hence evaluate the statistics as a base line for study of more widespread changes.

Variation of the cartilage is manifest mainly in the strip undergoing cytomorphosis. Extreme changes are rare in my material. This may be due to the widespread oral intake of vitamin supplements in infants and children. The thicknesses of the various zones of the cartilage lend themselves to rough measurements, and the results of our measurements are seen in figure 1. These show that there is a pronounced variation in the thickness of the growing cell zone. In general, this zone tends to diminish in thickness with age. The greatest change, as well as the greatest variation, is seen in the first year. Variation becomes quite small as the age of 2 to 4 years is reached, and thereafter significant variation of the thicknesses of the various zones have not been recognizable in the vast majority of the cases. In the age groups selected the variation is seen to be great in individual cases, but the trend toward diminution of thickness of the proliferating cell zone

9. Dodds, G. S., and Cameron, H. C.: Am. J. Anat. **55**:135, 1934; Am. J. Path. **14**:273, 1938; **15**:723, 1939.

with advancing age is quite evident. Fairly typical photomicrographs of the area, representing subjects of different ages (figs. 2 to 4), are provided to illustrate the progressive change in the proliferating cell zone. As would be expected, it is in the premature infant (fig. 2 *A*) at birth that the most marked variation is seen. This variation consists in irregularity of the line of penetration of the marrow vessels entering into the mature cartilage cell columns, irregularity of the calcification of the bony matrix as well as the matrix of the mature cell

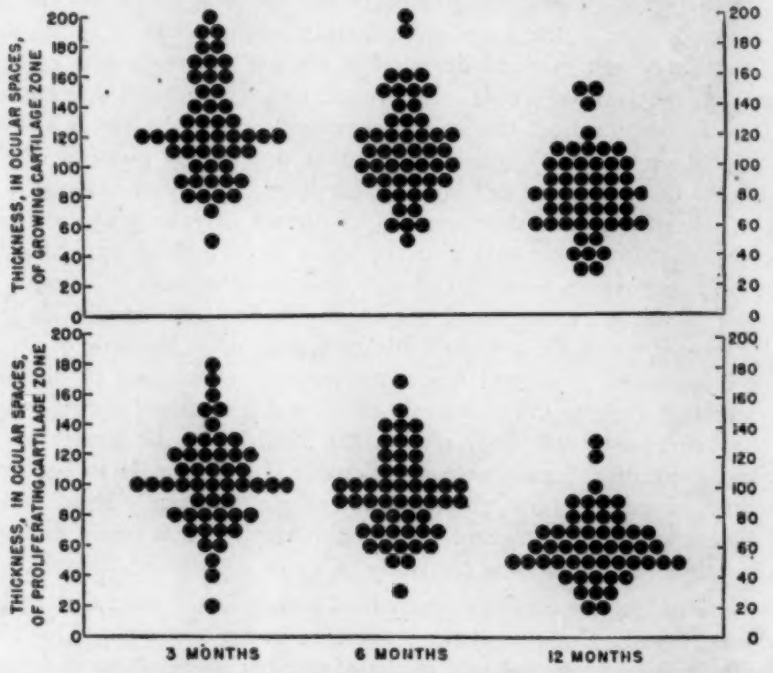

Fig. 1.—Manner in which the growth of rib cartilage varies with age. Rib sections were taken from postmortem material and grouped as follows: Those from infants aged from 2 to 4 months were designated as group A; those from infants aged 5 to 7 months, group B; those from infants aged 11 to 13 months, group C, and those from children aged 22 to 26 months, group D. When possible, the fifth, sixth or seventh rib was taken. The material was unselected as far as cause of death, duration of terminal illness and presence of nutritional factors were concerned. The cartilage was divided into (1) the resting cell zone, (2) the proliferating cell zone and (3) the mature cell zone. The demarcation between zone 1 and zone 2 was selected as a line drawn where the cartilage cells began to show multiplication—i. e., cells appeared in pairs and later in groups of four. The demarcation between zone 2 and zone 3 was selected as a line where the cells became mature—i. e., where the cells no longer continued to enlarge. The proliferative zone is the zone between the resting cells and the mature cells. Measurements were made with a calibrated ocular micrometer accurate to plus or minus 3 microns. The thickness, a measure of growth, is expressed in terms of ocular spaces, each of which equals 6.5 microns. The upper graph shows the distribution of the 50 cases each of groups A, B and C in regard to the thickness of zone 2 plus zone 3. The lower graph shows the distribution of these cases in regard to the thickness of zone 2 alone. Each dot represents one case.

zone and variation of the configuration of the mature cell zone such that often only suggestions of cell columns are evident. The growing and mature cell zones are often increased in thickness in prematurely born infants, but the growing cell zone is sometimes ill defined with respect to the resting cartilage because of the active division of the

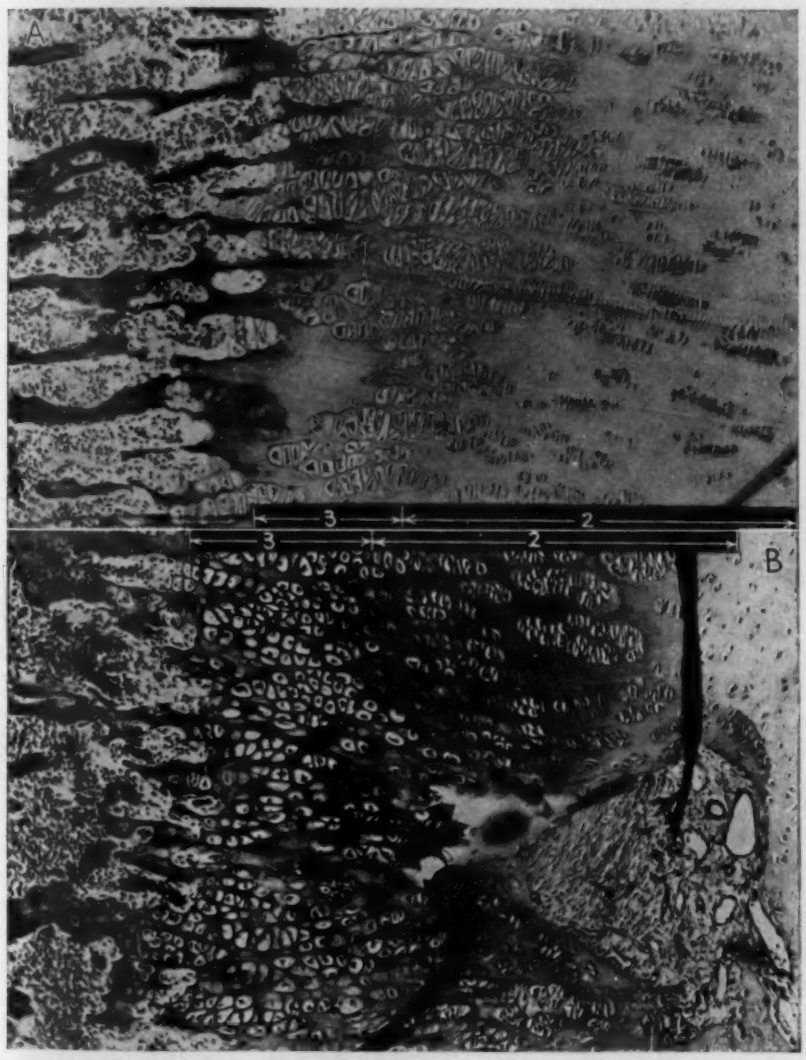

Fig. 2.—*A*, costochondral junction of a normal premature infant of seven months' gestation dying of cerebral hemorrhage. The numbers indicate zones as defined in the legend of figure 1.

B, costochondral junction of a normal 3 month old infant dying of influenzal meningitis. Note the large cartilage canals.

chondrocytes throughout the length of the costal cartilage. I include in the "normal" variation occurring in premature ribs the long trabeculae of calcified cartilage jutting into the marrow. These are common, and often small amounts of bone are deposited on all sides of these trabeculae. Active remodeling of premature ribs is sometimes seen, but usually one is impressed with the activity of the constructive processes and the relative insignificance of the osteoclastic ones. I interpret all these as expressions of the exceedingly rapid rate of growth—so rapid that there is little time for calcium to be deposited normally in cartilage and bone matrix, for mature cells to be normally penetrated by marrow or for the processes of remodeling to become manifest.

The photomicrographs representing the 3 month old (fig. 2*B*) and the older infants (figs. 3 and 4) show the deceleration in this rapid rate of growth, and the evidence of this deceleration is in the narrowing of the growing cell zone and in the degree to which this zone is demarcated from the resting zone. The cells in the resting zone are less active in these age groups, since here the stimulus toward growth is slowly decreasing This allows greater regularity in deposition of calcium, in remodeling, in removal of the calcified cartilage trabeculae of the bone marrow as they are replaced by bone, and in periosteal bone formation. These factors tend to make the bone tubular, with few cross trabeculae in its marrow cavity, and with a cortex regulated in thickness to the stress of movement of the rib.

My material does not show the matrix changes characteristic of the alterations of cartilage seen in articular cartilage or in the cartilage of adults. Atrophy, hyalinization, dropping out of cells, calcification of other than normal areas, fibrillation and liquefaction are not found. Changes such as these could not be expected in the absence of any joint surface in the immediate vicinity. Changes are seen frequently in the staining qualities of the cartilage matrix, and the most significant of them will be briefly mentioned. The most spectacular is the dark metachromatic staining of the whole cytomorphotic strip of cartilage which is found in long-standing disease such as glomerulonephritis and leukemia. Some have interpreted this as a sign of calcification, but calcium stains have not shown any calcium to be present except in the mature cell zone. I believe, as Hirsch [10] and Wislocki, Bunting and Dempsey [11] have suggested, that chemical changes occurring in the matrix are responsible for this difference of staining. Another anomaly of staining is the eosinophilic appearance of some strips of matrix adjoining the vessels of the cartilage canals on the distal periphery of the cartilage, already mentioned. Here I have found calcium to be

10. Hirsch, C.: Acta chir. Scandinav., 1944, supp. 83, p. 1

11. Wislocki, G. B.; Bunting, H., and Dempsey, E. W.: Am. J. Anat. **81**:1, 1947

deposited, and I ascribe this change and the deposition of calcium to the circulatory influence of nearby vessels. The mechanism of this deposition of calcium is not known, but the fact that alkaline phosphatase

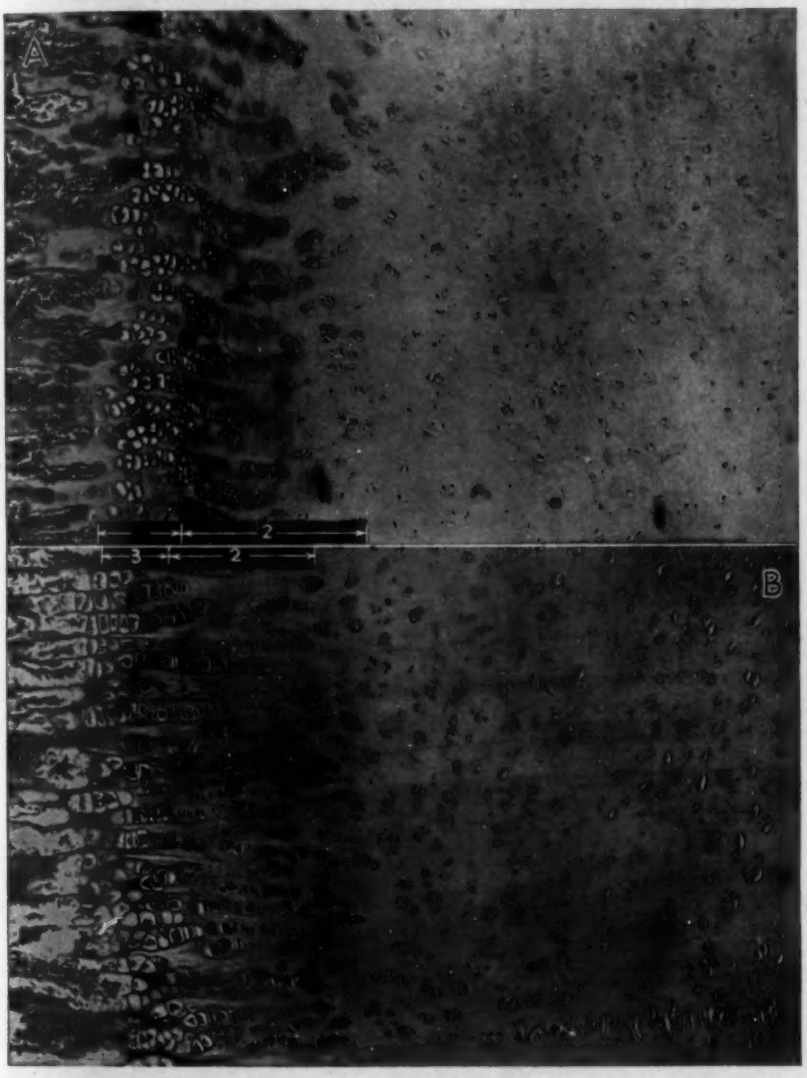

Fig. 3.—*A*, costochondral junction of a 5 month old infant dying suddenly of circulatory failure. The numbers indicate zones as defined in the legend of figure 1.

B, costochondral junction of a 14 month old child dying of complications of a surgical operation.

is present in the walls of the vessels, shown in phosphatase stains, may well have a bearing on this phenomenon.

In an effort to determine to what extent altered circulation affects the costochondral region, ribs were studied in 10 cases of coarctation of the aorta. In these cases the volume of blood circulating through

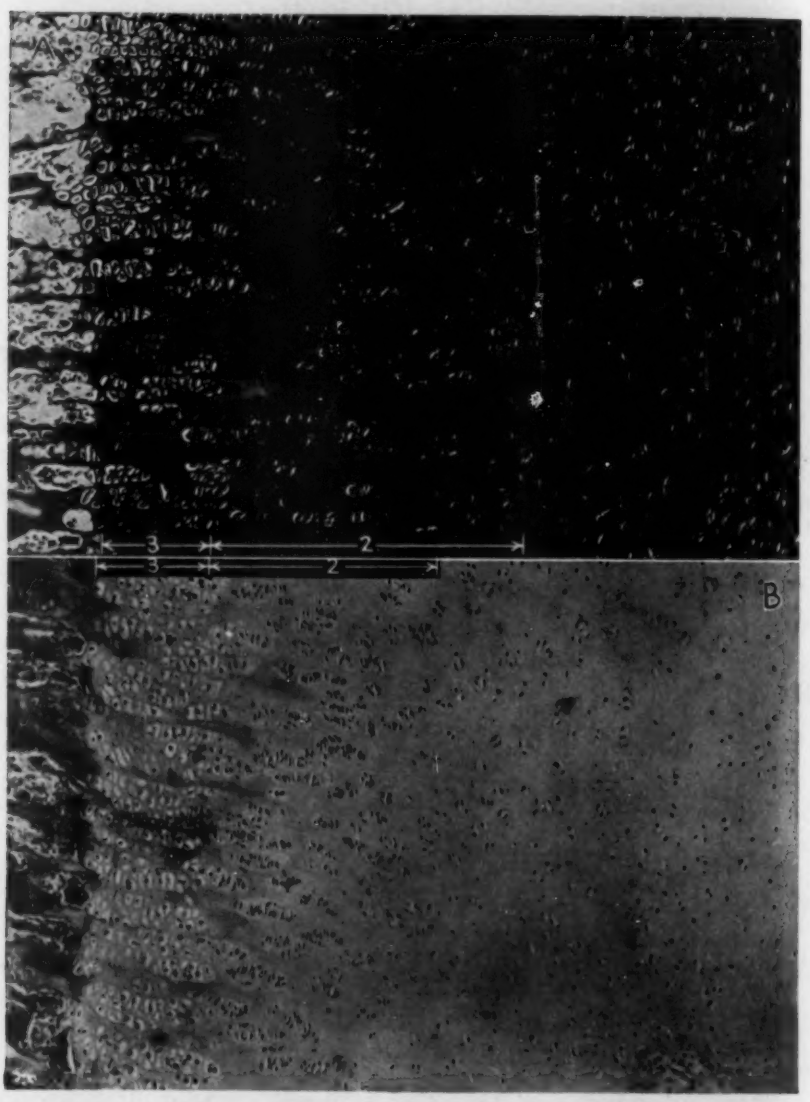

Fig. 4.—*A*, costochondral junction of a 2 year old child dying of influenzal meningitis. The numbers indicate zones as defined in the legend of figure 1.
B, costochondral junction of a 4 year old child dying of fulminating sepsis.

the anterior intercostal arteries to the aortic intercostal arteries was tremendously increased, these anastomoses providing the lower parts

of the aorta with most of their blood. The influence of such augmented circulation on the cytomorphotic zone was not adjudged to be great. No typical changes were found, although some disturbance of the sequence of growth was usually present. The disturbance is in the nature of a slowing of growth processes, whereas with the increase of blood flow an acceleration would be more likely if humoral factors alone were acting. This evidence suggests that the volume of blood flowing in this area does not regulate the sequence of growth.

ABNORMAL VARIATION

The main generalized conditions present in my material which are recognized as disease entities are scurvy, rickets, multiple vitamin deficiency, renal rickets, syphilis and lead poisoning. No histologic details of these well known entities were encountered other than those reported in the literature.[12] Two nonspecific entities, which I have called disturbance of growth and arrest of growth, have appeared much more frequently than the aforementioned diseases. The nonspecific disturbance of growth usually can be recognized by a much enlarged growing cell zone and a thickened mature cell zone with little evidence that the mature cells are being actively penetrated by the marrow vessels and connective tissue, and slight, if any, deposition of bone. The osteoid and calcium disturbance of rickets is not present, nor are the scorbutic stigmas present. In all, this variation is regarded as a temporary piling up of cartilage and a disturbance of the unknown mechanism by which it is converted into bone. The frequency with which this disturbance is observed in the presence of diverse acute diseases suggests that it is nonspecific. The correlation of the presence of this disturbance and that of acute severe disease and the dietary deficiencies of all necessary food elements accompanying the latter has been good.

Arrest of growth is usually seen in long-standing disease and here the microscopic picture of the cytomorphotic zone is one of extreme thinning of all zones, at the same time, instead of active marrow penetration, a thin band of osseous matrix is deposited in the lower ends of the mature cell columns, sealing them off, so to speak. The columns are never wholly sealed off, there being a few present with marrow vessels and cells at their extremities, but these may be sparse.

The characteristic changes of starvation noted in my material have corresponded in great degree to those described by Silberberg and Silberberg.[13] The material has not provided opportunity for a significant study of endocrine deficiency or hyperactivity.

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12. Park, E. A., Guild, H. G.; Jackson, D., and Bond, M.: Arch. Dis. Childhood **10**:265, 1935. Park, E. A.: The Pathology of Rickets, in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1939, vol. 34, p. 157. McLean, S.: Am. J Dis. Child. **41**:130, 363, 607, 887 and 1128, 1931.

13. Silberberg, M., and Silberberg, B.: Arch. Path. **30**:675, 1940.

SUMMARY

The anatomy of the costochondral junction has been presented as observed in children The sequences of its endochondral ossification have been studied and a detailed account of its vascular anatomy has been given, with emphasis on normal variability. The sequences of growth in this region are apparently independent of these variations in vascular anatomy. The variations resulting from coarctation of the aorta, also, do not produce characteristic changes. The growing cell zone when measured at various ages in infancy shows its thickness decreasing gradually with age during the first two years of life and later remaining approximately the same. The normal and the abnormal histologic variations of this region have been described.

It is emphasized that abnormal variations of nonspecific nature occur with much greater frequency than the well known entities affecting deposition of bone. These variations (distinct from rickets, scurvy, syphilis and other pathologic conditions) are here called disturbance of growth and arrest of growth, and each of these two histopathologic entities can be correlated with significant clinical data regarding generalized disease and nutrition.

Case Reports

FUEL OIL ASPIRATION PNEUMONIA

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NUMEROUS cases of pulmonary inflammation resulting from aspiration of medicinal liquid petrolatum have been reported since Laughlen,[1] of Toronto, Canada, recognized and described the condition in 1925. Pulmonary reaction following aspiration or ingestion of the less refined fractions of petroleum, however, are not so well known.

Coope [2] stated that a chronic proliferative inflammation of the lungs occurred in survivors of a torpedoed ship who had to swim in water contaminated with diesel oil. The remainder of the literature concerns children who had drunk kerosene or benzine (gasoline) and had aspirated the material directly or had inhaled vomitus containing ingested kerosene or benzine. Lesser and associates,[3] in their study of 22 cases in which children exhibited symptoms of kerosene intoxication severe enough to require their being hospitalized, collected over a two year period, noted roentgenologic evidence of pulmonary manifestations in 17, while there were only 5 in which physical signs of pulmonary involvement were present. The changes noted were interpreted as resulting from edema, hemorrhage and inflammation. The lesions described by Waring [4] in 9 of 23 cases ranged from mild bronchitis to fatal pneumonia. Most children with severe intoxications showed definite roentgenographic changes within a period of four hours. Other pulmonary complications recorded consisted of pneumothorax, pneumopericardium, emphysema and subcutaneous emphysema of the chest.[5] In all fatal cases there were definite clinical and roentgenographic evidences of pathologic changes occurring in the lungs, and Waring [4] felt that animal experimentation tended to confirm the clinical impression that pulmonary changes were the most important feature of the serious and fatal cases. Death usually occurred within eighteen hours, and beyond this period prognosis of survival improved.

Immediate effects of kerosene ingestion or inhalation are burning of the mouth and throat, spasm of the glottis, severe coughing and choking, retrosternal and epigastric pain, and frequent vomiting. Severe delayed manifestations following absorption are drowsiness, cerebral depression, muscle twitching, convulsions, coma, diarrhea, feeble and

From the Department of Pathology and Bacteriology, University of Toronto.

1. Laughlin, G. F.: Am. J. Path. **1**:407, 1925.
2. Coope, R.: Diseases of the Chest, Edinburgh, E. & S. Livingstone, 1945.
3. Lesser, L. I.; Weens, H. S., and McKey, J. D.: J. Pediat. **23**:352, 1943.
4. Waring, J. I.: Am. J. M. Sc. **185**:325, 1933.
5. (*a*) Lavenstein, A. F.: J. Pediat. **26**:395, 1945. (*b*) McNally, W. D.: Toxicology, Chicago, Industrial Medicine, 1937, p. 612. (*c*) Nunn, J. A., and Martin, F. M.: J. A. M. A. **103**:472, 1934. (*d*) Price, J. P.: ibid. **99**:214, 1932. (*e*) Scott, E. P.: J. Pediat. **25**:31, 1944. Lesser and others.[3]

rapid pulse, accelerated respirations, cyanosis, a moderately elevated temperature and acetonuria. Death may result from myocardial or hepatorenal insufficiency, but pneumonia usually terminates the picture.[6]

The production of the pulmonary lesions is thought by some authors to result only from aspiration of the material.[7] Deichmann and associates[6a] and Holt,[6c] the former on the basis of animal experimentation, expressed the belief that gastrointestinal absorption, with the noxious agent accumulating in the lung from the blood secondarily, is the important factor in the production of pulmonary lesions. The dose of kerosene required to produce the serious and fatal reactions in children has never been determined, but amounts as little as 3 or 4 ounces (88 to 118 cc.) are reported to produce death in young children.[5b] Poisoning has occurred in adults in industry from inhalation of fumes, but fatalities from any method of absorption are extremely rare. As much as a liter of kerosene has been ingested by an adult without causing death.[5b] Reports of cases in which autopsies have been made of children dying from either inhalation or ingestion of kerosene or fuel oil are rare in the literature. The following report is that of an adult exhibiting a fatal fulminating type of necrotizing pneumonia resulting from accidental inhalation and ingestion of fuel oil.

REPORT OF A CASE

A white man 44 years of age was admitted to the Toronto General Hospital on Dec. 22, 1942. In a lucid period the patient stated that at 2 a.m. the same morning he had "inhaled" an unknown quantity of "fuel oil" while attempting to clean an obstructed pipe of a stove used to heat his trailer. He coughed continuously and severely for approximately two hours, vomited several times and expectorated bloody mucus. Extreme weakness ensued, and the patient was discovered semiconscious by friends who brought him to the emergency department of the hospital.

At admission the man was markedly weak but otherwise examination revealed nothing abnormal. A gradual rise of pulse and respiratory rates occurred along with that of the temperature during the day. By 8 p.m. the temperature was 103.4 F., the pulse rate 118 and the respiratory rate 36. During this period a severe tearing pain occurred in the lower part of the right side of the chest, which further embarrassed his respirations, increasing the rate to 60. Because of the extreme respiratory difficulty, marked pallor and mental confusion, he was placed in an oxygen tent, with temporary relief of the orthopnea. However, restlessness, irritability and confusion persisted. The temperature stayed above 100 F., and the blood pressure ranged between 100 systolic and 62 diastolic and 60 systolic and 48 diastolic. Sulfadiazine was given the second day without affecting the course of the disease. At that time there was dulness over the lower and middle lobes of the right lung, with suppression of breath sounds, and distant moist rales were inconstantly heard over the lower half of the right lung. A roentgenogram showed consolidation of

6. (*a*) Deichmann, W. B.; Kitzmiller, K. V.; Witherup, S., and Johansmann, R.: Ann. Int. Med. **21**:803, 1944. (*b*) Farabaugh, C. L.: Minnesota Med. **19**: 780, 1936. (*c*) Holt, L. E., and MacIntosh, R.: Holt's Diseases of Infancy and Childhood, New York, D. Appleton-Century Company, Inc., 1940, p. 537. (*d*) Laughlen.[1] (*e*) Lesser and others.[3] (*f*) Lavenstein.[5a] (*g*) McNally.[5b] (*h*) Nunn and Martin.[5c] (*i*) Price.[5d]

7. Barbour, O.: J. A. M. A. **87**:488, 1926. Farabaugh.[6b] Lesser and others.[3] Nunn and Martin.[5c] Price.[5d] Waring.[4]

the lower lobes bilaterally and thickened pleura over the lower portion of the right lung. The patient gradually became weaker and died seventy-seven hours after admission.

There was albumin (2 and 3 plus) with occasional hyaline and granular casts in the urine. The serum nonprotein nitrogen was 76 mg. per 100 cc. After an initial rise of leukocytes to 19,000 per cubic millimeter of blood, with a differential distribution of 69 per cent neutrophils, 30 per cent lymphocytes and 1 per cent monocytes, the white cells fell to 9,900 per cubic millimeter the day before death

Autopsy.—The body was well nourished and well developed. In the left antecubital fossa there was a large bulla, and a superficial dry red ulcer, measuring 1.5 cm. in diameter, was seen on the lateral surface of the chest. Submandibular lymph nodes were slightly enlarged, but no other superficial lymph nodes were

Fig. 1.—Gross specimen of the necrotic middle lobe of the right lung which smelled strongly of fuel oil.

palpable. Postmortem lividity was marked in the dependent portions, and rigidity was still present.

About 400 cc. of slightly cloudy yellow fluid, suspended in which were many flakes of fibrin, was removed from the right thoracic cavity, and 100 cc. of clear yellow fluid from the left. A thin layer of fibrin covered the upper lobe of the right lung. Both lungs were greatly increased in weight, the right weighing 1,310 Gm. and the left 930 Gm. The middle lobe of the right lung was approximately three times its normal size and completely consolidated. Its pleural surface was made up of slightly raised confluent yellow nodules of varying size. The rough, finely shaggy cut surface smelled strongly of fuel oil and was composed entirely of ill defined separate and confluent yellow necrotic areas (fig. 1). Definite shaggy-walled abscesses filled with yellow purulent material were found in the majority of the necrotic zones. Similar necrotic consolidations were seen in the lower

anterior and posterior portions of the upper lobe of the left and the lower lobe of the right lung. The upper lobe tissue not involved in the consolidation was doughy and only slightly crepitant. The cut surfaces revealed massive edema and congestion. Superimposed on this in the airless lower lobes were many, irregular, dark purple, slightly depressed areas resembling patchy atelectasis. Most of the markedly congested bronchi were filled either with blood-stained fluid or thick yellow mucopurulent exudate. In the middle lobe of the right lung the terminal branches of the pulmonary artery were filled with yellow antemortem clot. The remainder of the pulmonary arteries were free of thrombi.

Numerous slightly raised thin black longitudinal striations were present in the lower 7 cm. of the esophagus. In the stomach there was generalized congestion with submucosal petechial hemorrhages.

The soft, flabby heart weighed 400 Gm. Petechial hemorrhages were scattered over the ventricular surfaces and throughout the myocardium but were most numerous in the left ventricular wall.

The enlarged liver weighed 1,860 Gm. The capsule was smooth and reddish brown. Congestion was noted on the cut surface, where the purple central areas were surrounded by yellow parenchyma.

The spleen, weighing 190 Gm., was slightly enlarged and soft. The reddish purple pulp was mushy.

The left kidney weighed 150 Gm. and the right 190 Gm. Congestion of the stellate veins and the protruding cut ends of small blood vessels were conspicuous on the kidney's cut surface.

Moderately soft enlargement of the mesenteric and retroperitoneal lymph nodes was noted. The marrow of the vertebrae was deep red and that of the femur yellow and fatty.

Permission to examine the nervous system was not granted.

Microscopic Examination.—Consolidated portions of the right lung, particularly of the middle lobe, stained with sudan IV, contained large amounts of oil. Most of the fat appeared as finely divided droplets in macrophages, but collections of larger globules were also free in the necrotic material and fibrin (fig. 2 *A*). Failure to reduce osmic acid indicated that most of the lipoid material was not animal fat but represented aspirated fuel oil of petroleum origin. Extensive necrotizing pneumonia was well demonstrated in the consolidated portions of the lung. Completely necrotic areas of irregular contour and various size were separated by bloodless hyaline alveolar walls enclosing fibrin, edema fluid and hemorrhage (fig. 2 *B*). The unusual feature of the necrotizing and inflammatory process was the paucity of inflammatory exudate, which consisted of a few macrophages, lymphocytes and polymorphonuclear leukocytes. Abscesses were larger and more numerous in bronchial regions, and most bronchial structures were destroyed except for remnants of edematous congested submucosal and muscular elements. Blood vessels, although the best preserved structures of the necrotic lung, were markedly damaged. Splitting of the layers by edema and hyaline necrosis of both arteries and veins made their disrupted walls blend into the surrounding tissue. Marked endothelial swelling of less severely involved arteries and arterioles greatly narrowed their lumens. Occasional large hemorrhages, so dense that all trace of lung structure was obliterated, occurred in non-necrotic but tremendously congested lung. In the lower lobe of the right lung layers of condensed red to reddish blue fibrin, varying greatly in thickness, were adherent to alveolar walls. Also in this region was the only typical area of bronchopneumonia, in which the inflammatory exudate consisted of closely packed polymorphonuclear leukocytes. Layers of fibrin enmeshing a few macrophages and lymphocytes were adherent to the pleural surfaces.

Large amounts of non-iron-reacting granular brown pigment were found in all of the pulmonary vessels... Just beneath the pleural surfaces covered by fibrin, pigment appeared as diffuse brown staining of the tissues. Similar brown granules were

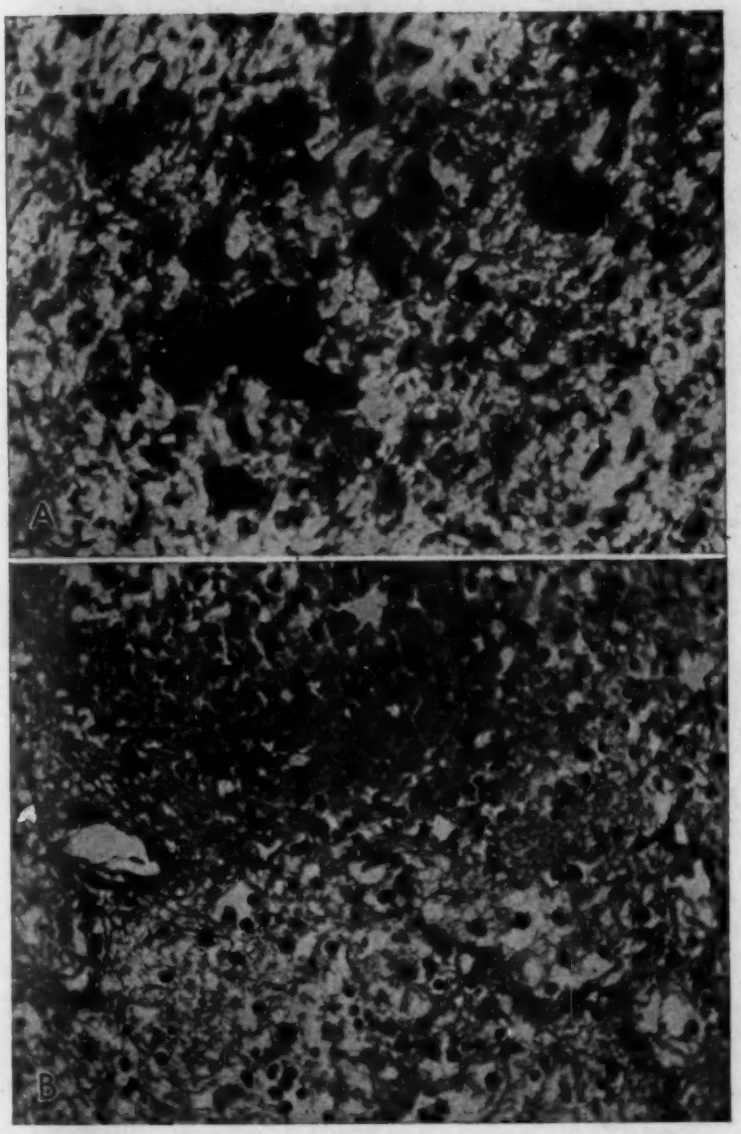

Fig. 2.—Oil droplets in completely necrotic lung, sudan iv; × 820.

diffusely distributed through other organs, particularly in the phagocytic cells of liver and spleen, and were suspended in the fat globules of parenchymal cells of the liver.

The greatly thickened mucosa and submucosa of the distal part of the esophagus was entirely necrotic except for several glandular collections and remnants of muscularis mucosae. Blood vessels at the surface blended into the necrotic tissue and were filled with hyaline plugs. Changes were seen in the veins similar to those in the necrotic lung, and there was swelling of arterial endothelium. The black streaks noted grossly were represented by superficial collections of non-iron-staining yellowish brown pigment, which closely resembled that seen in the blood vessels, the spleen and the liver. The inflammatory reaction of the necrotic ulcerated surfaces consisted of cellular infiltration, mainly lymphocytes and macrophages except in one area where polymorphonuclear leukocytes predominated. On the mediastinal surface was a thick fibrinous deposit in which was suspended a moderate amount of hemosiderin. Congestion of the submucosal vessels was the only microscopic abnormality in the stomach.

Fatty infiltration, consisting of both coarse and fine droplets, involved cells surrounding the central lobular veins of the liver. Liver cells proximal to the

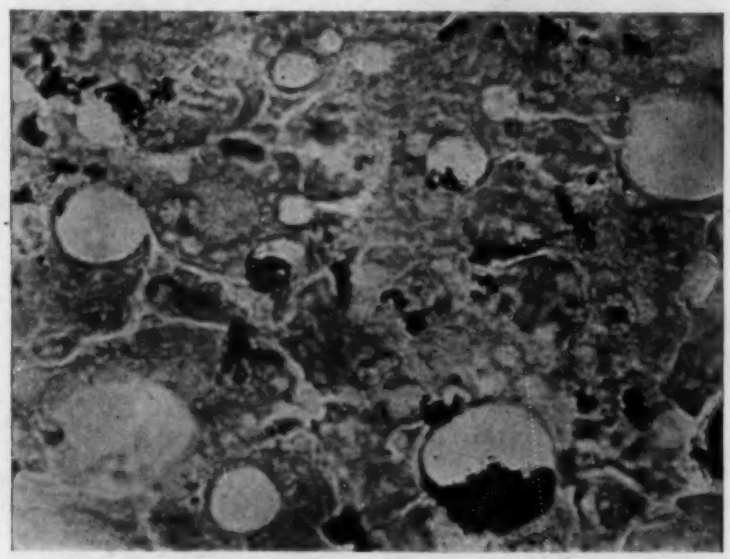

Fig. 3.—Non-iron-reacting brown pigment in Kupffer cells and suspended in fat droplets; prussian blue; × 750.

veins were the most severely affected, the process decreasing in severity as the lobular periphery was approached. Collections of yellowish brown pigment surrounded the collections of fatty liver cells. The pigment granules proved on prussian blue staining to consist both of hemosiderin and non-iron-staining material collected mainly as small granules in the Kupffer cells of the sinusoids. A moderate amount of non-iron-staining pigment was suspended in fat droplets of liver cells (fig. 3).

In addition to marked congestion of the splenic pulp, large amounts of phagocytosed pigment similar to that found in the liver were irregularly distributed throughout.

Moderate quantities of pink-staining granular material, resembling precipitated protein fluid, were noted in most of the glomerular spaces and proximal convoluted tubules. The kidneys were otherwise normal.

In spite of the necrotizing inflammatory process in the lung, no increase of myelocytes was observed in the bone marrow.

The remaining organs showed only varying amounts of yellowish brown pigment, scattered mainly throughout the veins.

COMMENT

The exact type and the source of the aspirated fuel oil were not known, but from all available information it fell into the kerosene light fuel oil bracket with boiling ranges between 340 and 560 F. In the Toronto district these oils are mixtures largely of aliphatic hydrocarbons of high boiling point and low volatility.

The lesions of the lung were characterized by large amounts of parenchymal destruction, congestion, hemorrhage and a tremendous outpouring of edema fluid and fibrin. The unusual feature was a poor cellular inflammatory reaction consisting mainly of macrophages, lymphocytes and varying numbers of polymorphonuclear leukocytes. This was in marked contrast to the case with autopsy presented by Deichmann and associates,[6a] in which a marked inflammatory exudate consisting mainly of polymorphonuclear leukocytes was a predominant finding. The other changes noted by him, including the formation of an alveolar hyaline membrane, were similar to those in our case.

The fuel oil was rapidly absorbed through the destroyed alveolar epithelium into the blood stream and may have had a marked toxic effect on the bone marrow and especially on the myelogenous elements. This is further emphasized by the first blood count, which showed, in spite of the total rise of leukocytes, a distribution of cells within normal limits, and by the marked secondary decrease of the circulating leukocytes the next day.

There is little doubt as to the genesis of the fatal pneumonitis in this case. The man's own definite statement and the very nature of the accident indicate that the material must have been aspirated directly into the bronchial tree. The absence of bronchial structures and the location of the most advanced necrotic lesions, which were in the bronchial regions, suggest direct inhalation as the mode of entry. Although marked ulceration of the esophagus and congestion of the gastric mucosa suggest that ingestion also occurred, the amount of material was hardly enough to produce fatal intoxication or to account for the extensive pneumonic lesion. The damage of the arteries, veins and capillaries was probably secondary to the extensive necrotic changes occurring in the surrounding lung parenchyma and not due to the effect of fuel oil transported from the gastrointestinal tract.

Consolidation was clinically detectable in the lower part of the right side of the chest thirty-six hours after inhalation, twelve hours after a tearing pain was felt in the same region. Roentgen examination confirmed the clinical findings and showed a marked pleural reaction in the lower part of the right side of the chest.

Damage to the circulating blood was evidenced not only by a decrease of the number of leukocytes but also by a large amount of yellowish brown pigment in the vessels, in hemorrhages of the lungs and other organs and deposits of large quantities in the liver and spleen. The non-iron-staining pigment recognized as granules or as brown staining of the tissue was considered to be hematin. Hematin does occur as a

product of intravascular hemolysis due to certain agents, such as an arsine (AsH_3), nitrobenzene, glyceryl trinitrate and aniline compounds. Wells [8] quoted Feigh as reporting that marked hematinemia occurs in acute toxic hemolysis and in many cases of poisoning with war gases. Deichmann and associates [6a] have found that non-necrotizing pulmonary lesions resembled grossly in many instances damage produced by inhalation of phosgene and hydrogen chloride. Instead of being broken down rapidly by hydrolysis into hemosiderin and hematoidin, hematin may be present for long periods and be destroyed slowly by oxidation. Moderate amounts of hemosiderin were also found in the Kupffer cells of the liver and in the fibrinous exudate of the esophageal serosa.

SUMMARY

Fatal necrotizing pneumonia resulted from aspiration of fuel oil in a 44 year old man. The pulmonary lesions were characterized by marked bronchial and peribronchial necrosis, edema, congestion, hemorrhages, fibrinous exudation and macrophagic and lymphocytic inflammatory response. The clinical history and the characteristics of the necrotizing process point to direct inhalation of the fuel oil.

A large amount of non-iron-staining pigment observed in the blood and tissue is considered most likely to have been hematin deposited in the course of acute toxic hemolysis.

8. Wells, H. G.: Chemical Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1920.

Notes and News

Appointments.—J. D. Kirshbaum, of Chicago, is now pathologist of the Kern General Hospital, Bakersfield, Calif.

P. R. Gerhardt, director of cancer control of the health department of West Virginia, has accepted the directorship of the New York State Cancer Division at Albany.

Deaths.—William Austin O'Brien, professor of public health in the University of Minnesota and director of the department of postgraduate medical education, at one time instructor in pathology, radio spokesman for Minnesota medical, dental and hospital associations, author of a syndicated health column and medical editor of the Newspaper Enterprise Association, died Nov. 15, 1947, aged 54.

Max Pinner, pathologist and specialist in tuberculosis, author of "Pulmonary Tuberculosis in the Adult," editor of the *American Review of Tuberculosis*, writer of articles on pathologic phases of tuberculosis, and in the course of years member of the staffs of various institutions in Chicago and other places, died Jan. 7, 1948, aged 57. In 1946 he was awarded the Trudeau Medal in recognition of his work on tuberculosis.

Society News.—The Federation of American Societies for Experimental Biology will meet in Atlantic City, N. J., on March 15 and following days.

The officers of the Michigan Pathological Society for 1948 are: A. A. Humphrey, Battle Creek, president; D. H. Kaump, Detroit, president-elect, and W. A. Stryker, Wyandotte, secretary-treasurer.

The American Public Health Association will hold its seventy-sixth annual meeting in Boston, Nov. 8 to 12, inclusive, 1948. The executive secretary is R. M. Atwater, 1790 Broadway, New York 19.

The American Society of Clinical Pathologists will hold its twenty-seventh annual meeting at the Drake Hotel, Chicago, Oct. 10 to 16, 1948. The annual seminar will be conducted by R. A. Moore, professor of pathology in Washington University, St. Louis, on "lesions of the male genito-urinary tract." Osborne A. Brines, Detroit, is the president-elect.

The Committee for Research in Problems of Sex.—Until March 15 next this committee will receive applications for grants-in-aid during the period July 1, 1948 to June 30, 1949. Application blanks may be obtained from the Division of Medical Science of the National Research Council, 2101 Constitution Avenue, Washington 25, D. C. George W. Corner, Carnegie Institution, Wolfe and Madison Streets, Baltimore, is now chairman of the committee, succeeding R. M. Yerkes, organizer, retired.

Awards.—Florence B. Seibert, associate professor of biochemistry in the Henry Phipps Institute, Philadelphia, has received the John Scott Medal of that city with a premium of $1,000 for her production of purified protein derivatives of tuberculin.

Benjamin S. Kline, pathologist at Mount Sinai Hospital, Cleveland, whose slide for syphilis is widely known, has received a gold medal from Phi Lambda Kappa associates.

Books Received

ENDOCRINOLOGY OF NEOPLASTIC DISEASES. A Symposium by Eighteen Authors. Edited by Gray H. Twombley, M.D., and George T. Pack, M.D. Cloth. Pp. 398, with 44 illustrations. Price $11. New York: Oxford University Press, 1947.

This symposium is an attempt to bring together answers to the "questions of what hormones there are, which ones produce cancer in animals and whether they produce cancer in men and women, too, what rare symptom complexes are due to functional tumors of the endocrine glands, and whether cancers can be ameliorated or cured by hormones. . . ." The monograph contains 16 chapters, each written by an authority, on hormonal aspects of tumors of the mammary gland, the pituitary gland, the uterus, the ovary, the prostate, the testis, the adrenal gland, the thyroid gland, the parathyroid glands, the pancreas and the pineal gland. The dilemma which faces the author of a book on this subject as to whether emphasis shall be on the role of hormones in tumorigenesis or on the hormonal effects of tumors is resolved by devoting almost equal space to each. The glandular therapy of tumors is not neglected.

It is inevitable in a book with many authors that the chapters vary in form, readability and thoroughness; in this book, some are comprehensive and critical reviews, while others are brief summaries. The general critical level is remarkably high. The format is pleasing, but in some places, as in chapter 3, the subheadings are defective. Omissions of subject matter are found, but on the whole they are of minor importance.

This book fills a need of long standing, and it can be highly recommended. Since this field is undergoing rapid changes, it is hoped that subsequent editions will keep the presentation of the various subjects up to date.

NEUTRON EFFECTS ON ANIMALS. By the Staff of the Biochemical Research Foundation; Dr. Ellice McDonald, director, Newark, Del. Pp. 198, illustrated. Price $3. Baltimore: Williams & Wilkins Company, 1947.

This book is a collection of scientific papers concerned with special chemical, physiologic and pathologic studies of the effects exerted by neutrons on bacteria, plants and animals. Bacteria and seedlings of plants were resistant to irradiation of a magnitude which produced profound effects in animals. In animals the principal physiologic changes were reduced consumption of food, sterility of males and greater susceptibility of young, small animals to irradiation. The reduced consumption of food which often led to great loss of weight, was attributed in part to gastric retention with decreased total acidity, decreased peptic activity and increased alkalinity of the gastric juice. Sterility of males and atrophy of seminiferous tubules were closely correlated, and these changes were not prevented by administration of alpha tocopherol (vitamin E). The chemical studies gave largely negative or inconclusive results. These studies involved investigations of: serum phosphatase; peroxidase, proteolytic and catalase activity in marrow; ribonuclease activity in blood, marrow and spleen; partition of the proteins of plasma and marrow.

The pathologic studies disclosed that in acute experiments severe effects were produced on the hemopoietic system at high dosage levels and that during chronic experiments subcutaneous tumors developed at low dosage levels in rats. The

damage done to the hemopoietic system was reflected principally by leukopenia, neutropenia and lymphopenia. The lymphocytes were the most susceptible of all cells. In lymphogenic organs atrophic changes were conspicuous. Other immature cells, especially in the marrow and the testes, were likewise susceptible but to a lesser degree. Hemorrhage, conspicuous in dogs, was unexplained. An important observation concerned the tumors developing in a high percentage of rats irradiated daily for several weeks at a low dosage level.

The data did not disclose any significant qualitative difference between the biologic effects of neutrons and those of roentgen rays. The studies as presented indicate the desirability of controlling experiments more accurately by complete nutritional, bacteriologic and pathologic observations.

HODGKIN'S DISEASE AND ALLIED DISORDERS. By Henry Jackson Jr., M.D., assistant professor of medicine, Harvard Medical School, and associate physician, Thorndyke Memorial Laboratory, Boston City Hospital; and Frederic Parker Jr., M.D., associate professor of pathology, Harvard Medical School, and pathologist in chief, Boston City Hospital. Pp. 172, illustrated. New York: Oxford University Press, 1947.

This book, the authors state, "is based largely on material collected over a period of years" from several Boston sources. It is in considerable measure a presentation of their personal views. This is especially true in regard to Hodgkin's disease, which they divide into paragranuloma, granuloma and sarcoma, thus confounding still further a state of affairs that is already sufficiently confused, since their division of the subject is apt to leave the impression that cases of Hodgkin's disease are separable into three clinical, anatomic and histologic groups. It is reminiscent of the days when paresis was called a parasyphilitic disease. As a matter of fact, in Hodgkin's disease one lymph node, in a given patient, may show the changes of "paragranuloma," a neighboring node those of "granuloma" and a third node those of "sarcoma," with signs of transition, one transforming into the other, while in addition, there may be nodes showing areas of hyalinization or healing. Until the cause of Hodgkin's disease is discovered it would seem wise to adhere to those histopathologic criteria which now serve adequately to distinguish Hodgkin's from other diseases and to omit efforts at compartmental arrangement. On page 7 the authors state that "in almost all cases" of Hodgkin's paragranuloma "the disease starts in the lymph nodes of the neck, to which the causative agent may have gained access through the pharynx." On page 19 the statement occurs that in Hodgkin's granuloma, "from autopsy studies of 63 cases, it is clear that the retroperitoneal and para-aortic lymph nodes were the most frequent primary site of the disease, followed by other lymph nodes. . . ." This may be construed either as contradictory or as a further attempt sharply to distinguish anatomically between Hodgkin's paragranuloma and Hodgkin's granuloma. In the latter event, many pathologists would probably hesitate to accept it, because the belief is now practically universally entertained that Hodgkin's disease is oftenest "primarily" or preponderantly a lesion of the deeper lymphoid structures and that it is rarely "primary" or preponderant in the superficial nodes, no matter how frequently enlargement of the superficial nodes may be the first clinically detectable sign of disease. Also, it is difficult to understand why plasmocytoma should be included as a condition allied to Hodgkin's disease while Briquet's so-called gastrointestinal pseudoleukemia is ignored, although it may simulate Hodgkin's disease clinically and anatomically and, indeed, has been referred to as a form of gastrointestinal Hodgkin's disease. Similarly, there is no description of the fibrotic or the hyperplastic changes which occur so commonly in the marrow in Hodgkin's

disease, and no consideration of the theory that the disease is primarily one of the marrow.

The authors state that in the so-called reticulum cell sarcoma the unit of growth is the macrophage, but no one appears to have shown that in this lesion the cells are phagocytic—and the macrophage, it would seem, is nothing if not phagocytic.

Other diseases described are lymphocytoma and lymphoblastoma, lymphosarcoma, giant follicle lymphoma and endothelioma. The authors state that "the leukemias as such should be treated by themselves . . ." and hence "we do not propose to discuss the leukemias except in so far as they are directly connected with some of the diseases considered." The authors maintain a healthy skepticism concerning primary endothelioma of lymph nodes and say, "we are in complete agreement with Willis's statement that '"endotheliomata" should be tolerated neither as a clinical nor as a biopsy histological diagnosis. . . .'" It should be emphasized that the atrocious term "biopsy histological diagnosis" is directly quoted from Willis and that Jackson and Parker are not responsible for it.

THE DANISH CANCER RESEARCHER—JOHANNES FIBIGER, PROFESSOR IN THE UNIVERSITY OF COPENHAGEN. By Knud Secher, physician in chief to the Bispebjerg Hospital and professor of clinical medicine. Pp. 206, illustrated. Copenhagen: Nyt Nordisk Forlag Arnold Busck (London: H. K. Lewis & Co., Ltd.), 1947.

This is a detailed authentic biography of the Danish pathologist Johannes Fibiger, 1867-1928, by one of his assistants. The introduction presents high points of the record of the distinguished Fibiger family, which probably made its way into Denmark from Germany about two hundred years ago. Then come descriptions of Johannes' early life, his training and development until his appointment as professor of pathology in the University of Copenhagen in 1900. Here, as well as elsewhere in the book, are many statements of historical interest concerning the development of teaching and research in pathologic anatomy in Denmark in relation to that in other countries, especially France, Austria and Germany. The rest, which is the main part of the book, deals with Fibiger's notable career and achievements as university professor and with his scientific work, especially, and thoroughly, with that on tuberculosis and cancer. At the end is an epilogue on his honors, followed by lists of his publications and of the references consulted by the biographer. There is an index of authors but not of subjects. The illustrations are well selected to show personal traits of Fibiger, an attractive personality, as well as features of special interest in connection with his studies on cancer. The English of the book is commendable in spite of occasional awkward turns.

Fibiger became an active member of the Danish cancer committee in 1907. In the same year his famous investigations of neoplastic formations in the stomach of the rat were started by the study of certain gastric growths of 3 wild rats imported from Dorpat. The course of subsequent events which led to the discovery of Gongylonema neoplasticum (Spiroptera neoplastica), a parasite of the cockroach, as a probable cause of papillomatous and carcinomatous proliferations of the rat stomach is given in accurate and consecutive detail (pp. 120-183). In 1913 Fibiger published his first report of "investigations concerning a nematode" and its ability to induce papillomatous and carcinomatous tumors in the ventricle of the rat, and in 1927 he received the Nobel prize in medicine for that work. Secher makes no undue claims for the final significance of Fibiger's work. He describes well the interest with which it was received and the difficulties encountered so far in the efforts to repeat it successfully. The book will be of great value to students of the methods and the history of experimental cancer research.